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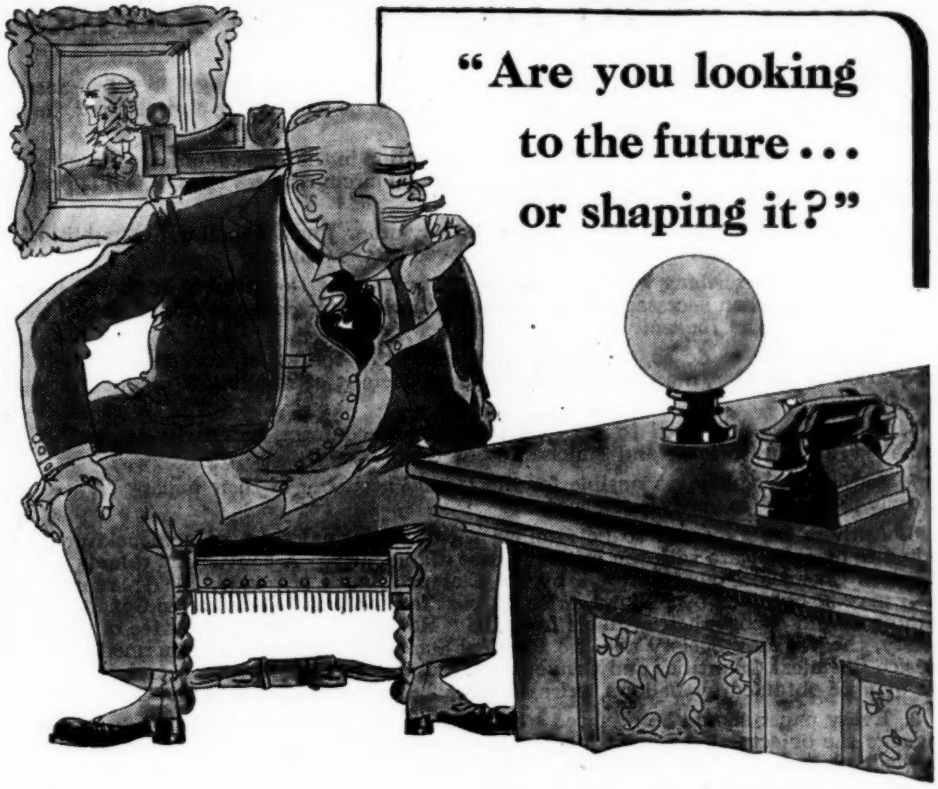

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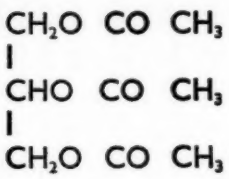

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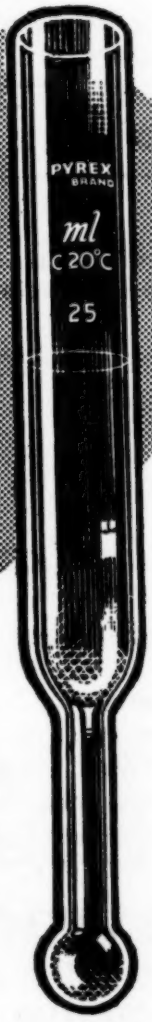

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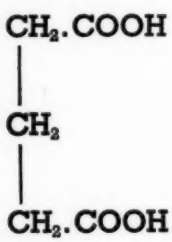

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ERRATA.

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601	In formula (V.)	*for* "CO·CO_2Et" *read* "CO_2Et".
803	8*	*for* "conditions. 1 : 1-Dichloro" *read* "conditions, 1 : 1-dichloro".
805	34	*for* "in 30 c.c. nitric acid (30 c.c. *d* 1·5)" *read* "(2 g.) in nitric acid (30 c.c., d_4 1·5)".
	44	*for* "$C_{14}H_4O_8Cl_4$" *read* "$C_{14}H_4O_8N_4Cl_4$".
	56	*for* "Bilz" *read* "Biltz".

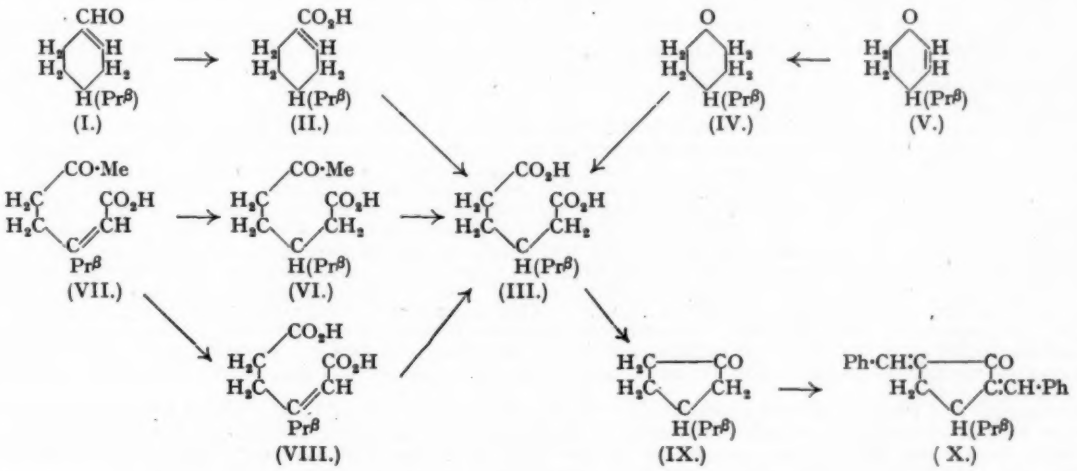
* From bottom.

40. *The Carbonyl Constituents of Eucalyptus Oils. Part IV. The Constitution of Phellandral.* d-, l-, *and* dl-β-iso*Propyladipic Acids.*

By G. Burger and A. Killen Macbeth.

The constitution of phellandral is verified by its oxidation to *β-iso*propyladipic acid. *d*- and *l*-Phellandral respectively yield *d*- and *l-β-iso*propyladipic acids, which, however, show no rotation although they yield a series of optically active derivatives. The *d*- and *l*-acids differ markedly in crystalline form and m. p. from *dl-β-iso*propyladipic acid, and the properties of corresponding derivatives are also distinct.

In a previous paper (Cooke, Macbeth, and Swanson, *J.*, 1940, 808) the 1 : 4 positions of the substituents in phellandral were confirmed by the conversion of the aldehyde into hexahydrocuminic acid, and the position of the ethylene linkage was indicated by the synthesis of *dl*-phellandric acid from α-bromohexahydrocuminic acid. Further support for the constitution has been sought in the oxidation of *l*-phellandral (I) through *l*-phellandric acid (II) to *l*-β-*iso*propyladipic acid (III). Analytical data indicated that the acid obtained was an *iso*propyladipic acid, but it showed no optical rotation when examined in acetone solutions of varying concentrations. It had, however, a different crystalline form and a considerably lower m. p. than *dl*-β-*iso*propyladipic acid prepared by the oxidation of dihydrocryptone (IV) obtained by the catalytic hydrogenation of cryptone (V) (Cahn, Penfold, and Simonsen, *J.*, 1931, 1366; Berry, Macbeth, and Swanson, *J.*, 1937, 986).



The identity and characteristics of *dl*-β-*iso*propyladipic acid were confirmed by its preparation by the catalytic hydrogenation of β-thujadicarboxylic acid (VIII) which was obtained from β-thujaketonic acid (VII) on oxidation with hypobromite; more satisfactory yields, however, were obtained by reduction of (VII) to δ-acetyl-β-*iso*propyl-*n*-valeric acid (VI) and oxidation of the latter.

dl-β-*iso*Propyladipic acid was further characterised by the preparation of its p-*chloro*- and p-*bromo-phenacyl esters*, and it was also converted into 3-*iso*propyl*cyclo*pentan-1-one (IX) and its dibenzylidene derivative (X) (cf. Wallach and Challenger, *Annalen*, 1911, **388**, 60).

Further examination showed that the acid obtained on the oxidation of *l*-phellandral was l-β-iso*propyladipic acid*, and that the absence of rotation, which at first caused some difficulty, was fortuitous. Braun and Werner (*Ber.*, 1929, **62**, 1050) prepared *dl*-β-*iso*propyladipic acid by the controlled oxidation with permanganate of *p-iso*propyl*cyclo*hexanol, and resolved the inactive acid into its *d*- and *l*-forms. No rotations were recorded for the free acids, and only remarkably low rotations were found in the case of the sodium salts and other derivatives. The m. ps. of all three acids were substantially lower than those we have found, and this causes some doubt concerning the purity of the acids (cf. Blanc, *Bull. Soc. chim.*, 1908, **3**, 294). *l*-β-*iso*Propyladipic acid was characterised by its p-*chloro*- and p-*bromo-phenacyl esters* both of which were optically active. It was also converted into *l*-3-*iso*propyl*cyclo*pentan-1-one which had a considerable *lævo*-rotation and gave an optically active *semicarbazone*. The ketone was further characterised by its 2 : 4-*dinitrophenylhydrazone* and by its *dibenzylidene derivative*, both of which have higher m. ps. than the corresponding derivatives of the *dl*-ketone.

The oxidation of a sample of *d*-phellandral (Berry, Macbeth, and Swanson, *J.*, 1937, 1448) in a similar way yielded *d*-β-*iso*propyladipic acid which gave an optically active *d*-3-*iso*propyl*cyclo*pentan-1-one. The *d*-ketone was characterised by its *semicarbazone*, 2 : 4-*dinitrophenylhydrazone*, and *dibenzylidene derivative*.

To complete the proof a sample of synthetic *dl*-phellandric acid was oxidised to *dl*-β-*iso*propyladipic acid identical with authentic samples obtained from dihydrocryptone and β-thujaketonic acid.

EXPERIMENTAL.

dl-β-iso*Propyladipic Acid.*—(a) *From β-thujaketonic acid.* The ketonic acid (10 g.) on oxidation by means of sodium hypobromite gave crude β-thujadicarboxylic acid (4·5 g.) which on recrystallisation from ether–ligroin had m. p. 115—116° (cf. Birch and Earl, *J. Proc. Roy. Soc. N.S.W.*, 1938, **72**, 55). β-Thujadicarboxylic acid (2·3 g.) in alcohol (40 c.c., 90%) containing palladised charcoal (0·5 g.) was hydrogenated at the laboratory temperatures; the reaction was slow and, during 3 days, the absorption of hydrogen (320 c.c.) was complete. After filtration and removal of solvent, a slowly crystallising oil (2·3 g.) remained; this, after distillation under high vacuum and crystallisation from ether–ligroin, gave *dl-iso*propyladipic acid, m. p. 81°, not depressed on admixture with a sample of the acid (m. p. 82—83°) obtained by the oxidation of dihydrocryptone (Found: C, 57·2; H, 8·5. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·6%).

(b) *From δ-acetyl-β-isopropyl-n-valeric acid.* β-Thujaketonic acid (2 g.) was hydrogenated at laboratory temperature in methanol containing palladised charcoal, complete absorption of hydrogen (275 c.c. at 25°/765 mm.) occurring within 30 mins. The resulting acid, a colourless oil (2 g.), was dissolved in sodium hydroxide (10 c.c., 5%) and added to bromine (2·8 c.c.) in sodium hydroxide (100 c.c., 6%) at 0°. After an hour in ice-water, the solution was extracted with ether, treated with a little sodium bisulphite solution and, after acidification, was exhaustively extracted with ether. An oil (1·8 g.), which subsequently crystallised, was obtained on removal of the solvent. On recrystallisation from water containing HCl it had m. p. 81—82°, not depressed on admixture with the above samples.

(c) *From* dl-*β-phellandric acid.* The acid (10 g.) dissolved in acetone (200 g.) at 0° was oxidised, whilst continuously stirred and kept at < 10°, by the gradual addition of finely powdered potassium permanganate. After the addition of the major part of the permanganate (25 g., 4 atoms oxygen) some water was added and further quantities of permanganate (4 g.) until the solution retained the pink colour for more than 30 mins. Excess permanganate was removed by addition of a little bisulphite, and the oxide sludge separated and well washed with hot water. After concentration of the combined filtrate and washings under reduced pressure, acidification of the concentrate, extraction with ether and removal of the solvent a clear oil (9 g.) was obtained which subsequently solidified. Distillation in high vacuum and recrystallisation from dilute hydrochloric acid gave *dl-β-iso*propyladipic acid, m. p. 82°, which was not depressed on admixture with the samples above (Found: C, 57·3; H, 8·4%).

p-*Bromophenacyl Ester of* dl-β-iso*Propyladipic Acid.*—This was prepared by the usual procedure. The resulting oil partly solidified; after it had remained on porous porcelain it was crystallised from alcohol giving the *ester*, m. p. 83° (Found: C, 51·5; H, 4·5; Br, 27·5. $C_{22}H_{24}O_6Br_2$ requires C, 51·5; H, 4·5; Br, 27·45%). The p-*chlorophenacyl ester* of *dl-β-iso*propyladipic acid was similarly prepared and had m. p. 65–67° (Found: C, 60·75; H, 5·2; Cl, 14·3. $C_{22}H_{24}O_6Cl_2$ requires C, 60·8; H, 5·3; Cl, 14·4%).

dl-3-iso*Propyl*cyclo*pentan*-1-*one.*—*dl-β-iso*Propyladipic acid (4·8 g.) was heated with barium hydroxide (0·5 g.) up to 110° in an air-bath during 40 mins. and the temperature then gradually raised to 200° during 30 mins. On raising the temperature to 250°, oil and water began to distil and the temperature was maintained at 250—260°. The collected oil (3·6 c.c.) was dissolved in 60% alcohol and the semicarbazone prepared by the addition of semicarbazide hydrochloride and potassium acetate. The semicarbazone (3·3 g.), after recrystallisation from alcohol, had m. p. 191—192°, and was optically inactive (Found: C, 59·1; H, 9·25. Calc. for $C_9H_{17}ON_3$: C, 59·0; H, 9·35%). The purified semicarbazone was steam-distilled in the presence of dilute sulphuric acid (50 c.c., 10%) and the distillate extracted with ether. After drying and removal of the solvent, the ketone remained as a colourless oil which had b. p. 184°/762 mm., $n_D^{18°}$ 1·4439, and was optically inactive. dl-3-iso*Propyl*cyclo*pentan*-1-*one*-2 : 4-*dinitrophenylhydrazone*, prepared in the usual way and recrystallised from alcohol, separated as yellow needles having m. p. 133—134° (Found: C, 54·9; H, 5·85. $C_{14}H_{18}O_4N_4$ requires C, 54·9; H, 5·9%). The dibenzylidene derivative was prepared by the addition of freshly distilled benzaldehyde (0·5 g.) to a solution of the ketone (0·0025 mol.) in a few c.c. of alcohol. The yellowish crystals were washed with a little alcohol and had m. p. 138° (Found: C, 87·2; H, 7·3. Calc. for $C_{22}H_{22}O$: C, 87·4; H, 7·3%) (cf. Wallach and Challenger, *loc. cit.*).

Oxidation of l-*Phellandral.* l-β-iso*Propyladipic Acid.*—*l*-Phellandral (20 g.) having $[\alpha]_D$ − 133·4° was dissolved in acetone (400 c.c.) cooled in ice and stirred mechanically during the gradual addition of finely powdered potassium permanganate at such a rate that the temperature did not rise above 10°. After the addition of some 40 g. of oxidant, ice-water was added to the reaction mixture and further permanganate (20 g.) added until the mixture had a permanent pink coloration. Filtration and thorough washing of the sludge with hot water followed by concentration of the combined filtrate and washings gave a separation of a little cuminic acid, m. p. 115°, on acidification. (In all phellandral oxidations some separation of cuminic acid was observed. This appears to be formed by oxidation of phellandral itself and not from traces of cuminal which might supposedly be present, since it has also been isolated in oxidation of phellandric acid.) Exhaustive extraction of the acidified concentrate with ether gave finally a syrupy oil (18·8 g.) which solidified to a waxy solid. Trituration with a little warm ligroin (60—90°) and suction-filtration gave a crystalline residue which when recrystallised from water yielded *l-β-iso*propyladipic acid, m. p. 73—73·5°. The m. p. could not be raised by further crystallisation; the m. p. was lowered on admixture with authentic samples of the *dl*-acid. Solutions of various concentration of the acid in acetone were optically inactive. The crystalline form was markedly different from that of the *dl*-acid (Found: C, 57·5; H, 8·55. Calc. for $C_9H_{16}O_4$: C, 57·4; H, 8·55%). The p-*chlorophenacyl ester* of *l-β-iso*propyladipic acid, prepared in the usual way, had m. p. 48—49°. It had $[\alpha]_D^{25°}$ − 9·43° in methanol (*c*, 0·9544) (Found: C, 60·65; H, 5·4; Cl, 14·25. $C_{22}H_{24}O_6Cl_2$ requires C, 60·8; H, 5·3; Cl, 14·4%). The p-*bromophenacyl ester* had m. p. 63—64° and $[\alpha]_D^{25}$ − 7·41° in alcohol (*c*, 1·8896) (Found: C, 51·6; H, 4·6; Br, 27·4. $C_{22}H_{24}O_6Br_2$ requires C, 51·4; H, 4·5; Br, 27·45%).

l-3-iso*Propyl*cyclo*pentan*-1-*one.* *l-β-iso*Propyladipic acid (5·6 g.) and barium hydroxide (0·5 g.) when distilled as described for the *dl*-acid yielded a pale yellow-green oil (4 c.c.) which, after purification through the semicarbazone, gave the pure *l*-ketone, b. p. 183°/761 mm., $n_D^{18°}$ 1·4443 and $[\alpha]_D^{20°}$ −191·3° in alcohol (*c*, 5·1172). The *semicarbazone* of the *l*-ketone had m. p. 191—192° and $[\alpha]_D^{20°}$ −76·4° in acetone (*c*, 0·2722) (Found: C, 59·2; H, 9·45; N, 22·95. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·35; N, 22·95%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 137° (Found: C, 54·9; H, 5·85. $C_{14}H_{18}O_4N_4$ requires C, 54·85; H, 5·9%). The *dibenzylidene derivative* of the *l*-ketone had m. p. 149—150° (Found: C, 87·3; H, 7·3. $C_{22}H_{22}O$ requires C, 87·4; H, 7·35%).

Oxidation of d-*Phellandric Acid.* d-β-iso*Propyladipic Acid.*—*d*-Phellandric acid (3·3 g.) in acetone (80 c.c.) was oxidised as described above. The product was an oil (3·4 g.) which did not crystallise. It was treated with hot water and filtered from a small amount of insoluble oil and cuminic acid (0·24 g.). The concentrated filtrate was exhaustively extracted with ether and, after removal of the solvent, the solidified residue was left on porous porcelain. The product was recrystallised from dilute hydrochloric acid and *d-β-iso*propyladipic acid (0·9 g.) obtained. It had m. p. 72—73° and its crystalline form was similar to that of the *l*-acid (Found: C, 57·3; H, 8·4. Calc.: C, 57·4; H, 8·6%).

d-3-iso*Propyl*cyclo*pentan*-1-*one.*—*d-β-iso*Propyladipic acid (0·8 g.) when distilled with barium hydroxide (0·2 g.) gave the crude ketone (0·45 g.) which when purified through the semicarbazone gave the pure *d*-ketone as a colourless oil having the characteristic odour and b. p. 183°/760 mm., $n_D^{17°}$ 1·4438, and $[\alpha]_D^{17°}$ + 190° in alcohol (*c*, 1·0052). The *semicarbazone* of the *d*-ketone, prepared in the usual way, had m. p. 191° (Found: C, 59·05; 9·35. $C_9H_{17}ON_3$ requires C,

59·0; H, 9·35%). The 2 : 4-*dinitrophenylhydrazone*, pale yellow needles, had m. p. 136° (Found: C, 55·0, H, 6·0. $C_{14}H_{18}O_4N_4$ requires C, 54·85; H, 5·9%). The *dibenzylidene derivative* had m. p. 149—150° (Found: C, 87·2; H, 7·3. $C_{23}H_{22}O$ requires C, 87·4; H, 7·35%).

We are indebted to Professor Earl for a gift of the β-thujaketonic acid, and one of us (G. B.) wishes to thank the Carnegie Corporation of New York for assistance which enabled him to participate in the work.

JOHNSON CHEMICAL LABORATORIES, UNIVERSITY OF ADELAIDE. [*Received, July 23rd*, 1945.]

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41. *Amidines. Part I. Preparation of Amidines from Cyanides.*

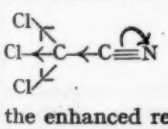
By P. OXLEY and W. F. SHORT.

Amidines and their *N*-monosubstituted derivatives may be prepared by heating the ammonium or alkyl- or aryl-ammonium salt of an aromatic or aliphatic sulphonic acid with a cyanide at 180—300°. α-Naphthamidine and *o*-substituted benzamidines can be prepared in this way.

ALTHOUGH amidines have been obtained by a variety of methods only three are important as methods of preparation. Pinner's method (*Ber.*, 1877, **10**, 1889; "Die Imidoäther," 1892) involves the use of large volumes of anhydrous solvents and cannot be applied to the preparation of *o*-substituted benzamidines or of α-naphthamidines since the corresponding cyanides cannot be converted into imino-ethers. *o*-Ethoxyphenyl cyanide, however, affords an imino-ether in poor yield (Pinner and Dietz, *Ber.*, 1890, **23**, 2942) and a 40% yield of *o*-hydroxybenziminoethyl ether hydrochloride is obtained from *o*-hydroxyphenyl cyanide (Easson and Pyman, *J.*, 1931, 2999). Methods of preparation depending on the production of an imido- or amido-chloride (Gerhardt, *Annalen*, 1858, **108**, 217; Hofmann, *J. pr. Chem.*, 1866, **97**, 267; Klinger, *Annalen*, 1876, **184**, 280; Lossen, Mierau, Kobbert, and Grabowski, *Annalen*, 1891, **265**, 129; v. Pechmann, *Ber.*, 1895, **28**, 2362; 1897, **30**, 1782; Walther and Grossmann, *J. pr. Chem.*, 1908, **78**, 478; Hill and Cox, *J. Amer. Chem. Soc.*, 1926, **48**, 732; Sen and Rây, *J.*, 1926, 646; Pyman and Chew, *J.*, 1927, 2318) frequently afford good yields of amidines when applied to substituted amides of aromatic acids, but anomalous results are usually obtained with the substituted amides of aliphatic acids (Wallach, *Annalen*, 1877, **184**, 1; v. Braun, Jostes, and Heymons, *Ber.*, 1927, **60**, 92; Heymons, *Ber.*, 1932, **65**, 320; v. Braun and Rudolph, *Ber.*, 1934, **67**, 269, 1762; v. Braun, *Angew. Chem.*, 1934, **47**, 611). Walther and Grossmann (*loc. cit.*) showed that aromatic amines react with cyanides in presence of sodium to give sodio-amidines, and unsubstituted amidines may frequently be obtained from cyanides and sodamide or potassamide (Cornell, *J. Amer. Chem. Soc.*, 1928, **50**, 3313; Ziegler, Rohm, and Haas, G.P. 641,125; U.S.P., 2,049,582; Ziegler and Ohlinger, *Annalen*, 1932, **495**, 84; Kirsanov and Polyakova, *Bull. Soc. chim.*, 1936, **3**, 1600; May and Baker, Ewins, Newbery and Ashley, B.P. 538,463; May and Baker, Ewins and Ashley, B.P. 545,708. Cf. Vermillion and Hauser, *J. Org. Chem.*, 1941, **6**, 507). The method is not a general one and good yields are usually obtained only from aromatic cyanides and trisubstituted cyanides, $CR_3{\cdot}CN$, which cannot yield by-products by reacting in the enimic form. It is stated in almost all the standard text-books of organic chemistry that amidines may be prepared by heating cyanides with ammonium chloride, but this statement appears to be an extrapolation of Bernthsen's discovery (*Annalen*, 1877, **184**, 290; 1878, **192**, 1) that *N*-aryl- and *NN*-diaryl-amidines may be prepared by heating a cyanide with the hydrochloride of a primary aromatic amine or of diphenylamine. (See also Walther and Grossmann, *loc. cit.*; Scholl, *Monatsh.*, 1918, **39**, 238.) Bernthsen expressly stated that amidines could not be obtained from cyanides and ammonium chloride. Very small yields of amidines have subsequently been obtained by heating acetamide with ammonium nitrate and liquid ammonia (Fichter, *Z. Elektrochem.*, 1912, **18**, 651; *Verh. Naturf. Ges. Basel*, 1913, **23**, 221) and from cyanides by heating under pressure with ammonium chloride and liquid ammonia (Cornell, *loc. cit.*).

A number of new methods for the preparation of substituted and unsubstituted amidines of the open chain, cyclic, and semicyclic type will be described in this series of memoirs, and we now record the preparation of amidines and their *N*-monosubstituted derivatives by heating the ammonium or alkyl- or aryl-ammonium salt of an aromatic or aliphatic sulphonic acid with a cyanide at a suitable temperature within the range 180—300°.

There is no record of the production of an amidine by the addition of ammonia or an amine to an unsubstituted cyanide,* but the introduction of certain polar atoms or groups stimulates the cyano-group so that addition occurs. Thus, Curtis and Nickell (*J. Amer. Chem. Soc.*, 1913, **35**, 887) found that amidines are produced by the addition of diethylamine, di-*n*-propylamine, or benzylamine to ethyl cyanotartronate, $(CO_2Et)_2C(OH){\cdot}CN$, and trichloromethyl cyanide adds ammonia and amines at low temperatures to give trichloroacetamidine and its derivatives (I.G., G.P. 671,785). It seems evident that in these compounds the kationoid properties of the unsaturated carbon of the cyano-group are enhanced by the inductive effect of the substituents and a similar activation doubtless accounts for the enhanced reactivity of trichloromethyl cyanide in the Hoesch reaction and for the alkaline hydrolysis of chloral and trichloroacetic acid. We suggest that the additive capacity of the cyano-group may also be



* The statement that *N*-*o*-chlorophenylbenzamidine is obtained in 75% yield by heating phenyl cyanide and *o*-chloroaniline at 180° (Walther and Grossmann, *loc. cit.*, p. 491) is probably due to a typographical error, since repetition of the experiment failed to yield any amidine. The amine hydrochloride was probably used as in all other cases reported in the paper.

enhanced by an " imported " stimulus and that the reaction between a cyanide and a salt of a sulphonic acid may be represented as follows :—

$$R{\cdot}C{\equiv}N' + R'{\cdot}SO_2O\}^{\ominus}\ R''\overset{\oplus}{N}H_3 \rightleftharpoons R{\cdot}C\langle^{N^-}_{O{\cdot}SO_2R'}\}^{\ominus}R''\overset{\oplus}{N}H_3\ (I.) \rightleftarrows R{\cdot}C\langle^{NH_2}_{NHR''}\}^{\oplus}R'{\cdot}SO_2O^{\ominus}\ (II.)$$

The salient features are the production of (i) a complex anion (cf. I) capable of degrading the ammonium ion (cf. the decomposition of ammonium nitrite), probably by hydrogen bond formation between the nitrogen atoms, (ii) the amidine salt of a strong acid. An alternative mechanism postulating the dissociation of the ammonium salt and ammonolysis of the intermediate, $R{\cdot}C(:NH){\cdot}O{\cdot}SO_2R'$, is unacceptable since no ammonia is liberated during the reaction and the intermediate would not be stable at the temperature employed (see Part II). An equilibrium is established between *p*-cyanophenyl methyl sulphone, ammonium benzenesulphonate, and the benzenesulphonate of *p*-amidinophenyl methyl sulphone, and the constituents are readily isolated in this case owing to the absence of by-products. The equilibrium constants have been determined at 250—255° and at 258—260° by isolating the amidine produced from mixtures of the cyanide with the ammonium salt (Table I); the experimental errors involved are too large to allow the heat of reaction to be calculated.

TABLE I.

Temp.	250—255°		258—260° (*a*)	
Mols. of $Ph{\cdot}SO_2NH_4$.	Yield of amidine, %.	Equilibrium constant.	Yield of amidine, %.	Equilibrium constant.
1·0	48	2·70	47·5 (*b*)	2·64
1·5	55	2·49	56·9	2·73
2·0	61	2·69	61·3 (*c*)	2·73
2·5	—	—	63·5	2·67
3·0 (*d*)	64	2·53	64·0	2·53

Notes.—(*a*) We are indebted to Dr. M. W. Partridge for the determinations at 258—260°.
(*b*) 47% of the amidine salt remains when the salt is heated at 260° for 2 hours.
(*c*) The value 60·2% is obtained when the equilibrium is approached from the other side.
(*d*) Mixtures containing more than 3·0 mols. of ammonium salt are not homogeneous.
Equilibrium is attained in 2 hours in all cases.

This method for the preparation of amidines has been widely applied and the results are shown in Table II. The influence of temperature, time of reaction, and proportion of reactants on the yield of amidine has not been thoroughly examined in all cases, so that the yields recorded in Table II are not necessarily the highest obtainable. It will be noted that primary aromatic amines afford either a *N*-mono- or a *NN'*-di-arylamidine as main product, so that the amine sulphonates behave in the same way as the hydrochlorides (Bernthsen, *loc. cit.*). The ammonium salts of a variety of sulphonic acids may be employed and in some cases the use of a salt of an alkanesulphonic acid is advantageous owing to the lower m. p. and the greater solubility of the cyanide in the melt. The fact that ammonium chloride gives very low yields of amidines even under special conditions is doubtless connected with its infusibility and its inability to yield homogeneous mixtures with cyanides. The use of other ammonium salts and of other nitrogen compounds in the preparation of amidines will be described in later communications. The formation of amidines from phenyl cyanides is usually promoted by groups which act as electron-sinks (*p*-$MeSO_2$·, *p*-Br, *p*-NO_2) and is retarded by those which act as electron-sources. This may mean that amidine formation is analogous to the production of cyanohydrins (Lapworth), but an electron displacement which accelerates the formation of (I) will retard its rearrangement to (II) at a higher temperature. In the absence of a detailed physico-chemical investigation, it is impossible to decide which is the rate-determining stage of the reaction. The observation that, in general, amidine formation is more complete with the salts of weak bases agrees with the reaction mechanism suggested, since the corresponding ammonium ion will be more prone to degradation.

This method of producing amidines is applicable to α-naphthyl cyanide and *o*-substituted phenyl cyanides, thus rendering accessible amidines not easily made by other methods, and can be used in the preparation of monoamidines from dicyanides. It has the advantage of being a one-stage process which can be operated without employing a solvent. Unchanged cyanide and excess of the ammonium salt are readily separated and recovered from the reaction product. Substances which may be regarded as potential sources of cyanides under the conditions of the reaction may be used in place of cyanides, but the yield of amidine is usually lower owing to side reactions. Thus, benzamide and ammonium benzenesulphonate (1·1 mol.) afford benzamidine benzenesulphonate (4%) when heated at 250° for 3 hours.

EXPERIMENTAL.*

The cyanide and the salt of the sulphonic acid are heated, preferably with stirring, under the conditions specified in Table II; the use of sealed tubes is unnecessary except in the case of volatile cyanides such as phenyl cyanide. A homogeneous melt is usually produced at the outset but, in a few cases, the mixture only becomes homogeneous as the reaction proceeds. The isolation of the amidine salt and liberation of the free amidine are effected by known methods. The amidine benzenesulphonates in general are less soluble in cold water than the corresponding hydrochlorides, and it is often possible to extract unchanged cyanide from the reaction product with acetone or ether and then separate the residual

* See also Boots Pure Drug Co. Ltd., Oxley and Short, B.P. 573,266 (27.1.1944).

TABLE II.

Amidine.	Ammonium or amine benzenesulphonate mols.	Reaction Temp.	Reaction Time, hrs.	Yield of amidine, %.	Amidine benzenesulphonate. M. p.	Formula.	Found, N, %.	Required.
(1) Benzamidine	4·0	270—280°	20	66	175—175·5°	—	—	—
(2) *N*-Phenylbenzamidine	1·0	270	0·25	81·5	—	—	—	—
(3) *NN*-Diphenylbenzamidine	1·0	200—210	0·33	29	243	$C_{25}H_{22}O_3N_2S$	6·55	6·5
(4) *N*-*p*-Tolylbenzamidine	1·0	240	0·17	84	184	—	—	—
(5) *NN'*-Di-*p*-tolylbenzamidine	2·5	270	1·0	86	217	—	—	—
(6) *N*-*p*-Nitrophenylbenzamidine	1·1	240	0·25	30	258 (decomp.)	$C_{19}H_{17}O_5N_3S$	10·7	10·5
(7) 4-*Bromobenzamidine*	1·0	250—260	2·0	52	257	$C_{13}H_{13}O_3N_2BrS$	8·1	7·8
(8) 4-Methoxybenzamidine	1·0	260—270	1·0	18	212	$C_{14}H_{16}O_4N_2S$	9·15	9·1
(9) 4-Amidinophenyl methyl sulphide	1·2	270	1·0	49	—	—	—	—
(10) 4-Amidinophenyl methyl sulphone	2·5	258—260	2·0	63·5	253	$C_{14}H_{14}O_6N_2S_2$	8·0	7·9
(11) *N*-Ethyl-4-amidinophenyl methyl sulphone	1·0	275—280	1·3	41	—	—	—	—
(12) *p*-Sulphonamidobenzamidine	1·4	250—255	2·0	67	—	—	—	—
(13) *N*-4'-Sulphonamidophenyl-4-sulphonamidobenzamidine	1·0	230	0·5	45	—	—	—	—
(14) *o*-Nitrobenzamidine	1·9	250	2·5	12·5	213·5	$C_{13}H_{13}O_5N_3S$	13·2	13·0
(15) *m*-Nitrobenzamidine	1·06	245—250	2·0	34·5	203·5	—	—	—
(16) *p*-Nitrobenzamidine	1·06	255—260	2·0	43·5	258·5	—	—	—
(17) α-Naphthamidine	1·7	260—270	2·0	29	210—211	$C_{17}H_{15}O_3N_2S$	8·7	8·5
(18) β-Naphthamidine	2·2	250	2·0	25	203	—	—	—
(19) 2-Amidinopyridine	1·4	265—270	1·25	49	145·5	$C_{12}H_{12}O_3N_3S$	15·2	15·05
(20) 3-Amidinopyridine	1·2	250—255	4·5	18	185—185·5	$C_{12}H_{12}O_3N_3S$	15·0, 15·0	15·05
(21) Phenylacetamidine	1·33	260—270	3·0	54·5	186—186·5	—	—	—
(22) *N*-*o*-Chlorophenylphenylacetamidine	1·0	230—235	0·5	100	—	—	—	—
(23) *N*-Methylphenylacetamidine	1·1	240—280	1·0	57	—	—	—	—
(24) *N*-Benzylphenylacetamidine	1·1	245—295	1·0	62	131	—	—	—
(25) *N*-*p*-Tolylphenylacetamidine	1·0	240	0·17	73	—	—	—	—
(26) αγ-Diamidinopropane	2·0	235—240	1·0	50	197	$C_{17}H_{24}O_6N_4S_2$	12·55	12·6
(27) 1 : 11-Diamidinoundecane	4·0	260—265	3·0	—	—	—	—	—
(28) α-4-Amidinophenoxy-β-4'-cyanophenoxyethane	1·0	260	2·0	22	239—239·5	$C_{22}H_{21}O_4N_3S$	10·2	9·6
(29) 4 : 4'-Diamidino-αβ-diphenoxyethane	3·0	260	3·0	57	>270	$C_{28}H_{30}O_8N_4S_2$	10·0	9·1
(30) 4 : 4'-Diamidino-αγ-diphenoxypropane	4·0	260—270	2·75	39	236—237	$C_{29}H_{32}O_8N_4S_2$	8·9	8·9
(31) 4 : 4'-Diamidinostilbene	6·0	275—280	2·0	47	—	—	—	—
(32) 4 : 4'-Diamidinodiphenyl sulphone	4·6	270	1·0	57	—	—	—	—
(33) 4-Amidino-4'-cyanodiphenyl disulphoxide	4·0	245—250	2·0	50	245—247	$C_{26}H_{17}O_8N_3S_3$	8·95	8·85

Notes.—(1) Rouiller (*Amer. Chem. J.*, 1912, **47**, 483) states that the benzenesulphonate has m. p. 173°. The picrate had m. p. 238—239° (Found: N, 20·2. Calc. for $C_{13}H_{11}O_7N_5$: N, 20·1%); Dieckmann (*Ber.*, 1892, **25**, 547) gives m. p. 228°. The trichloroacetate had m. p. 126° decomp. (Pinner, "Imidoäther") records m. p. 127° (decomp.).

(2) The amidine had m. p. 116° (Brunner, Seeger, and Dittrich, *Monatsh.*, 1924, **45**, 69, give m. p. 113·5°) and the hydrochloride, m. p. 231° (Lossen, *Annalen*, 1891, **265**, 138, gives m. p. 224°). *NN'*-Diphenylbenzamidine (15%), m. p. 147° (Busch and Falco, *Ber.*, 1910, **43**, 2559, record m. p. 144°), was simultaneously formed.

(3) A mixture of diphenylamine, benzenesulphonic acid, and phenyl cyanide was employed. The amidine had m. p. 113—113·5° (Brunner, Seeger, and Dittrich, *loc. cit.*, give m. p. 112°) and the nitrate, 220° (decomp.) (Bernthsen, *Annalen*, 1878, **192**, 13, gives m. p. 213—215° (decomp.)).

(4) The amidine had m. p. 100·5—101° (Bernthsen, *Annalen*, 1876, **184**, 355, gives 99—99·5°).

(5) Prepared from *p*-toluidine benzenesulphonate. *N*-*p*-Tolylbenzamidine benzenesulphonate was simultaneously obtained in 4% yield. *NN'*-Di-*p*-tolylbenzamidine had m. p. 131—132° (Bernthsen, *loc. cit.*, gives m. p. 131°), and the hydrochloride, m. p. 240—241° (decomp.)).

(6) The amidine had m. p. 168°; Barber (*J.*, 1943, 103) records m. p. 167—168°.

(7) The *amidine* had m. p. 159° (decomp.) (Found: N, 13·6. $C_7H_7N_2Br$ requires N, 14·1%) and the *picrate*, 272° (decomp.) (Found: N, 16·1. $C_{13}H_{10}O_7N_5Br$ requires N, 16·4%). Andrewes, King, and Walker (*Proc. Roy. Soc.*, 1946, *B*, **133**, 20) describe the hydrochloride, m. p. 264—265°.

(8) *p*-Methoxybenzamidine had m. p. 119° (Found: N, 18·5. Calc. for $C_8H_{10}ON_2$: N, 18·7%). Lossen and Grabowsky (*Annalen*, 1897, **297**, 385) record m. p. 112°. The *picrate* had m. p. 213° (Found: N, 18·4. $C_{14}H_{13}O_8N_5$ requires N, 18·5%).

(9) Prepared by Dr. A. Koebner. The hydrochloride had m. p. 218—220° (Found: N, 13·7. Calc. for $C_8H_{11}N_2ClS$: N, 13·8%). Fuller, Tonkin, and Walker (*J.*, 1945, 633) record m. p. 218—219°.

(10) The hydrochloride had m. p. 294° (Found: N, 11·9; Cl, 15·1. Calc. for $C_8H_{11}O_2N_2ClS$: N, 11·9; Cl, 15·1%) in agreement with Fuller, Tonkin, and Walker (*loc. cit.*). Andrewes, King, and Walker (*loc. cit.*) record m. p. 288—289°.

(11) Prepared from ethylamine benzenesulphonate. The *picrate* had m. p. 155·5—156° (Found: N, 15·4. $C_{14}H_{17}O_9N_5S$ requires N, 15·4%) and the *toluene-p-sulphonate*, m. p. 242° (Found: C, 51·15; H, 5·6; N, 7·2 $C_{17}H_{22}O_3N_2S_2$ requires C, 51·25; H, 5·6; N, 7·0%).

(12) The free base, m. p. 223° (decomp.), and the hydrochloride hemihydrate, m. p. 250—252°, did not depress the m. p.'s of specimens prepared as described by Levene, Pyman, and Boots Pure Drug Co. (B.P. 544,836 of 1941). Delaby and Harispe (*Bull. Soc. chim.*, 1943, **10**, 580) state that the base and anhydrous hydrochloride melt at 251° and 242° respectively; Andrewes, King, and Walker (*loc. cit.*) give m. p. 228° decomp. as the m. p. of the base and 250—251° as that of the hydrochloride hemihydrate. Ammonium methane-, toluene-*p*-, *m*- and *p*-nitrobenzene-, naphthalene-α- and naphthalene-β-sulphonates were also used in the preparation of this amidine.

(13) The amidine had m. p. >270°; the *hydrochloride*, m. p. 288·5° (decomp.), was hydrated (Found, on sample dried at 100°: N, 14·3. $C_{13}H_{13}O_4N_4ClS_2$, requires N, 14·3%).

(14) The *picrate* had m. p. 232—233° (decomp.) (Found: N, 21·3. $C_{19}H_{15}O_9N_9$ requires 21·3%).

(15) Rouiller (*loc. cit.*, p. 491) records m. p. 198—200° for the benzenesulphonate.

(16) Rouiller (*loc. cit.*) states that the benzenesulphonate has m. p. 250°. The *picrate* melts at 240° (Found: N, 21·5. $C_{13}H_{10}O_9N_8$ requires N, 21·3%).

(17) α-Naphthamidine had m. p. 154° and its picrate m. p. 226·5°; Ponzio and Zanardi-Lamberti (*Gazzetta*, 1923, **53**, 818) record 154° and 223° respectively.

(18) β-Naphthamidine had m. p. 136° (Lossen and Grabowski, *Annalen*, 1897, **297**, 381, give m. p. 145°, and Kirsanov and Polvakova, *Bull. Soc. chim.*, 1936, **3**, 1606, give m. p. 133—136°); the picrate melted at 247°; Ponzio and Zanardi-Lamberti (*loc. cit.*), give m. p. 240°.

(19) The picrate had m. p. 207·5—208°.

(20) Barber and Slack (*J. Amer. Chem. Soc.*, 1944, **66**, 1607) have prepared nicotinamidine hydrochloride, m. p. 190°, by the Pinner method, and Andrewes, King, and Walker (*loc. cit.*) record m. p. 189—190°.

(21) Rouiller (*loc. cit.*, p. 492) records m. p. 182—183° for the benzenesulphonate.

(22) The amidine had m. p. 111·5—112° (Found: N, 11·55. Calc. for $C_{14}H_{13}N_2Cl$: N, 11·45%). The *picrate* had m. p. 153—153·5° (Found: N, 14·75. $C_{20}H_{16}O_7N_8Cl$ requires N, 14·8%).

(23) The free base was an oil; the *Reineckate* separated from 30% aqueous acetone in plates, m. p. *ca.* 137° (Found: SCN, 49·6, 49·7. $C_{15}H_{19}N_6S_4Cr$ requires SCN, 49·7%).

(24) In agreement with Neber and Uber (*Annalen*, 1928, **467**, 52) the free base had m. p. 93°. These authors give benzenesulphonate, m. p. 127—130°.

(25) The free base had m. p. 119°; Bernthsen (*Annalen*, 1876, **184**, 346) gives m. p. 118—119°.

(26) Preparation by Dr. J. Cymerman. The *di-picrate* had m. p. 235° (Found: N, 23·4. $C_{17}H_{16}O_{14}N_{10}$ requires N, 23·9%).

(27) The yield of crude amidine was good but purification losses were high. The picrate, m. p. 190—192°, did not depress the m. p. of a specimen prepared as described by King, Lourie, and Yorke (*Lancet*, 1937, **233**, 1360).

(28) The *picrate* had m. p. 202° (Found: N, 16·4. $C_{25}H_{18}O_{14}N_8$ requires N, 16·5%).

(29) The free base had m. p. 228° (decomp.) and the *picrate*, m. p. >270° (Found: N, 18·3. $C_{32}H_{24}O_{14}N_8$ requires N, 18·5%). May and Baker, Ewins, Barber, Newbery, Ashley and Self (B.P. 507,565; *J.*, 1942, 110) record 231—232° (decomp.) and 234—235° (decomp.) as the m. p. of the free base.

(30) Preparation by Dr. M. W. Partridge. The amidine has been prepared by May and Baker, Ewins, *et al.* (*loc. cit.*).

(31) Preparation by Mr. S. W. Stroud. The dihydrochloride had m. p. >360° after drying at 60° under reduced pressure (Found: N, 16·5. Calc. for $C_{16}H_{18}N_4,2HCl$: N, 16·6%). This amidine has been described by May and Baker, Ewins and Ashley (B.P. 510,097; *J.*, 1942, 110).

(32) Preparation by Dr. A. Koebner. The dihydrochloride, m. p. 300—302°, did not depress the m. p. of a specimen prepared as described by Ashley, *et al.* (*loc. cit.*, p. 110).

(33) Preparation by Dr. J. Cymerman.

mixture of amidine and ammonium salts by crystallisation from water or alcohol. The sulphonic acid salts of the substituted amidines are often sparingly soluble in water and, since they do not crystallise readily from aqueous solutions,

it is often preferable to employ alcohol as solvent. Alternatively, the free amidine may be liberated by the addition of ammonia or 5N-sodium hydroxide to an aqueous or alcoholic solution or suspension of the salt. The free base is collected by filtration or in a suitable solvent (*e.g.*, chloroform) and may then be separated from unchanged cyanide by solution in hydrochloric acid. Aqueous solutions of the sulphonic acid salts of ammonia and amidines frequently dissolve considerable amounts of cyanides which are almost insoluble in water.

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[*Received, August 25th*, 1945.]

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42. *Attempts to find New Antimalarials. Part XXIII. Derivatives of 3 : 4 : 2′ : 3′-Pyridoacridine and 1 : 2 : 2′ : 3′-Pyridoacridine.*

By JAMES DOBSON and WILLIAM O. KERMACK.

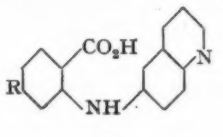
(6′-Quinolyl)anthranilic acid and 4-chloro-(6′-quinolyl)anthranilic acid (from 6-aminoquinoline and *o*-chlorobenzoic acid or 2 : 4-dichlorobenzoic acid) have been cyclised to yield 5-*chloro*-3 : 4 : 2′ : 3′-*pyridoacridine* and 5 : 8-*dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine* respectively. By condensing these compounds with the appropriate dialkylaminoalkylamine, a series of derivatives of 3 : 4 : 2′ : 3′-pyridoacridine has been obtained carrying a basic side-chain in the 5-position. These all show a definite antimalarial activity when tested on *P. gallinaceum* infections of chicks, and this action is particularly marked when a chlorine atom is present in the 8-position of the acridine nucleus. From 8-aminoquinoline or 8-amino-6-methoxyquinoline on the one hand and *o*-chlorobenzoic acid or 2 : 4-dichlorobenzoic acid on the other, 5-*chloro*-1 : 2 : 2′ : 3′-*pyridoacridine* and its 8-*chloro*-, 4-*methoxy*-, and 8-*chloro*-4-*methoxy*-derivatives have been synthesised. The chlorine atom in position 5 in these four compounds has been replaced by diethylaminoethylamino and diethylamino*iso*amylamino groups, but none of the bases of this series, tested biologically, showed antimalarial activity.

THE chief synthetic antimalarial compounds, plasmoquin (pamaquin) and atebrin (mepacrine hydrochloride), are derivatives of quinoline and acridine respectively, and both carry the same basic side-chain, namely, diethylamino*iso*amylamino. Extensive investigations have shown that antiplasmodial activity is retained when the structure of the side-chain is varied over wide limits. In the quinoline series, the side-chain need not be in the 8-position as in plasmoquin, for compounds with the side-chain in position 4 or 6 are also stated to be active to some extent. So far, however, attempts to obtain active compounds of the same general type as atebrin and plasmoquin, but based on some other heterocyclic nucleus have not been very successful. For example, various phenanthridine derivatives have been prepared by Walls (*J.*, 1934, 104; 1935, 1405), but these were without antimalarial activity, and derivatives of *p*- and *m*-phenanthroline have been prepared by Kermack and Weatherhead (*J.*, 1940, 1164) and Kermack and Webster (*J.*, 1942, 213) but none of those tested showed unambiguous activity. Certain compounds of the same general class derived from benzoquinoline and *p*- and *m*-phenanthroline are described in the patent literature (B.P. 451,932, 454,525, 481,874; G.P. 668,968) and in one or two instances claims of action on blood parasites are made.

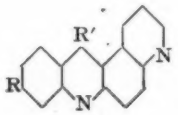
The object of the work now described was to prepare a series of pyridoacridine derivatives carrying a basic side-chain in the 5-position of the acridine nucleus, the position corresponding with that which it occupies in atebrin. 6-Aminoquinoline was condensed in amyl alcohol solution with potassium 2 : 4-dichlorobenzoate (1 mol.) in presence of a trace of copper bronze. When the resulting 4-chloro-(6′-quinolyl)anthranilic acid (I; R = Cl) was refluxed with phosphorus oxychloride it was cyclised and converted into 5 : 8-*dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine* (II; R = Cl, R′ = Cl). The latter was somewhat difficult to purify because of the ease with which the 5-chlorine atom was hydrolysed with the formation of the 8-*chloro*-5-*hydroxypyridoacridine* (II; R = Cl, R′ = OH), or in the alternative isomeric form, 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone (III; R = Cl). For example, when refluxed in ethyl alcohol containing less than one per cent. of water, it dissolved, but on cooling a crystalline material separated, shown to be 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone hydrochloride, and partial hydrolysis occurred even on refluxing with ordinary benzene. The chloropyridoacridone was rapidly formed from the dichloropyridoacridine when it was boiled with dilute mineral acid; but the dichloro-pyridoacridine is very stable in the presence of dilute sodium hydroxide. In keeping with this stability to alkali, the 5-chloro-pyridoacridines reacted very slowly when heated or refluxed with bases such as diethylaminoethylamine, but the reaction proceeded satisfactorily in phenol solution, as with 5-chloroacridine and its derivatives (cf. B.P. 363,392). In this way, 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine was condensed with the following bases: diethylaminoethylamine, diethylaminopropylamine, 2-amino-5-diethylaminopentane, dimethylaminopropylamine, butylaminopropylamine and diethylaminobutylamine. Of the resulting compounds 8-*chloro*-5-(β-*diethylaminoethyl*)*amino*-, 8-*chloro*-5-(γ-*diethylaminopropyl*)*amino*-, 8-*chloro*-5-(γ-*dimethylaminopropyl*)*amino*-, and 8-*chloro*-5-(γ-*butylaminopropyl*)*amino*-3 : 4 : 2′ : 3′-*pyridoacridine* were isolated as crystalline solids; the others were obtained as thick oils which were purified through their *picrates* or *dinitrobenzoates*, from which the bases could be readily recovered on decomposing with sodium hydroxide and extracting with ether.

These bases resemble atebrin in containing a chlorine atom in the 8-position of the acridine nucleus: it was of interest to prepare compounds analogous to the above but without the chlorine atom. 6-Aminoquinoline was condensed with *o*-chlorobenzoic acid and the resulting (6′-quinolyl)anthranilic acid (I; R = H) cyclised with phosphorus oxychloride to yield 5-*chloro*-3 : 4 : 2′ : 3′-*pyridoacridine* (II; R = H, R′ = Cl), a compound which was readily hydrolysed in presence of dilute mineral acid to give 3 : 4 : 2′ : 3′-*pyridoacridone*,

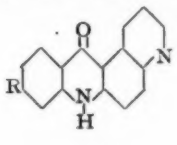
but which was very stable to alkali. This acridone was also prepared directly from (6′-quinolyl)-anthranilic acid by treatment with concentrated sulphuric acid at 100°. 5-Chloropyridoacridine was readily condensed



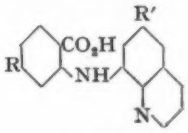
(I.)



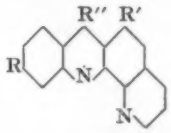
(II.)



(III.)



(IV.)



(V.)

in phenol solution with diethylaminoethylamine and 2-amino-5-diethylaminopentane with the formation of the corresponding *bases* (II; R = H, R′ = NH·[CH$_2$]$_2$·NEt$_2$, NH·CHMe·[CH$_2$]$_3$·NEt$_2$) of which the former was obtained as a crystalline solid, whilst the latter was isolated as the *picrate*.

In addition to the bases containing the 3 : 4 : 2′ : 3′-pyridoacridine nucleus, some derivatives have also been prepared of the isomeric 1 : 2 : 2′ : 3′-pyridoacridine. 8-Aminoquinoline was condensed with *o*-chlorobenzoic acid and with 2 : 4-dichlorobenzoic acid to yield (8′-quinolyl)anthranilic acid (IV; R = H, R′ = H) and 4-chloro-(8′-quinolyl)anthranilic acid (IV; R = Cl, R′ = H) respectively. These acids are readily cyclised with phosphorus oxychloride to form *5-chloro-* (V; R = H, R′ = H, R″ = Cl) and 5 : 8-*dichloro*-1 : 2 : 2′ : 3′-*pyridoacridine* (V; R = Cl, R′ = H, R″ = Cl). Like the 5-chloropyridoacridines of the previous series, these compounds undergo hydrolysis of the 5-chlorine atom very readily, 1 : 2 : 2′ : 3′-*pyridoacridone*, and its 8-*chloro*-derivative being formed on heating to 100° with mineral acid, and even on refluxing for 1—2 hrs. with alcohol. 1 : 2 : 2′ : 3′-Pyridoacridone is also formed on heating the (8′-quinolyl)-anthranilic acid with sulphuric acid on the boiling water bath.

An analogous series of compounds was obtained when 8-aminoquinoline was replaced by 8-amino-6-methoxyquinoline. In this way there were prepared (6′-methoxy-8′-quinolyl)anthranilic acid (IV; R = H, R′ = OMe) and 4-chloro-(6′-methoxy-8′-quinolyl)anthranilic acid (IV; R = Cl, R′ = OMe) which yielded 5-*chloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* (V; R = H, R′ = OMe, R″ = Cl) and 5 : 8-*dichloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* (V; R = Cl, R′ = OMe, R″ = Cl) respectively, and also the corresponding 4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridone* and 8-*chloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridone*. In general, these resembled in appearance and properties the analogous compounds without the methoxy group.

5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine and its 8-chloro-, 4-methoxy-, and 8-chloro-4-methoxy-derivatives have been condensed with β-diethylaminoethylamine and 2-amino-5-diethylaminopentane. Thus the following eight bases have been synthesised: 5-(β-diethylaminoethyl)amino-1 : 2 : 2′ : 3′-pyridoacridine, 5-(δ-diethylamino-α-methylbutyl)amino-1 : 2 : 2′ : 3′-pyridoacridine, 8-*chloro*-5-(β-*diethylaminoethyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine*, 8-*chloro*-5-(δ-*diethylamino*-α-*methylbutyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine*, 5-(β-diethylaminoethyl)-amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, 5-(δ-diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, 8-*chloro*-5-(β-*diethylaminoethyl*)*amino*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* and 8-chloro-5-(δ-diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine. These were analysed either as free bases or as *picrates*.

Antimalarial tests were carried out on *P. gallinaceum* infections of chicks in the Biological Laboratories of Imperial Chemical Industries Ltd. Full details of the biological tests will be published elsewhere. The activities of some of the compounds are shown in the Table, the activity at various doses being indicated as negative (−), slight (±) or marked (++).

Reference No.	Formula of base.	Dose, mg./kg.	Activity.
M.3574	V; R = R′ = H, R″ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	125	−
M.3476	V; R = Cl, R′ = H, R″ = NH·[CH$_2$]$_2$·NEt$_2$	125	−
M.3303	V; R = Cl, R′ = H, R″ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	125	−
M.3599	V; R = H, R′ = OMe, R″ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	125	−
M.3477	V; R = Cl, R′ = OMe, R″ = NH·[CH$_2$]$_2$·NEt$_2$	125	−
M.3533	V; R = Cl, R′ = OMe, R″ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	200	−
		125	±
M.3302	II; R = H, R′ = NH·[CH$_2$]$_2$·NEt$_2$	125	+
M.3561	II; R = H, R′ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	125	+
		80	+
M.4582	II; R = Cl, R′ = NH·[CH$_2$]$_4$·NEt$_2$	120	+
		80	+
		40	−
M.3652	II; R = Cl, R′ = NH·[CH$_2$]$_2$·NEt$_2$	120	++
		80	+
		40	−
M.3902	II; R = Cl, R′ = NH·[CH$_2$]$_3$·NMe$_2$	120	++
		40	+
M.3304	II; R = Cl, R′ = NH·[CH$_2$]$_2$·NEt$_2$	125	++
M.3555	II; R = Cl, R′ = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	125	++
		80	++
		40	+
M.4344	II; R = Cl, R′ = NH·[CH$_2$]$_3$·NHBu	120	++
		40	+
		20	±

It will be seen that the derivatives of 1 : 2 : 2′ : 3′-pyridoacridine are inactive, and that all the bases containing the 3 : 4 : 2′ : 3′-pyridoacridine nucleus exhibit antimalarial activity. This is relatively feeble in the absence of a chlorine atom in the 8-position but, when this chlorine atom is present, all the bases tested are relatively potent.

Experimental.

4-Chloro-(6′-quinolyl)anthranilic Acid.—Potassium 2 : 4-dichlorobenzoate (45·8 g.), 6-aminoquinoline (28·8 g.), amyl alcohol (50 c.c.) and copper bronze (0·3 g.) were refluxed in an oil bath at 150° for 6 hours. The brown residue was separated and washed with acetone. The solid material was dissolved in a large volume of hot dilute ammonia solution and, after filtering, the filtrate was acidified with acetic acid giving a brown–yellow precipitate of 4-chloro-(6′-quinolyl)-anthranilic acid in relatively small yield. A further quantity was obtained by treating the residue with hot 2N-HCl and filtering the hot solution. The orange hydrochloride of 4-chloro-(6′-quinolyl)anthranilic acid separated, and, after filtration, was suspended in water and carefully neutralised with ammonia. The acid (42·3 g.) was crystallised from ethyl alcohol in yellow needles, m. p. 266°. 4-Chloro-(6′-quinolyl)anthranilic acid was soluble in cold dilute alkali and in hot alcohol and benzene. It gave sodium or potassium salts, separating from concentrated sodium or potassium hydroxide solutions.

The ethyl ester was prepared by refluxing the acid (3 g.) with ethyl alcohol (20 c.c.) and concentrated sulphuric acid (10 c.c.) for 4 hours. The cooled solution was poured into ice-water, filtered and made alkaline with ammonia. A dark red oily substance separated which solidified (2·3 g.) on treatment with dilute sodium bicarbonate solution. *Ethyl 4-chloro-(6′-quinolyl)anthranilate*, crystallised twice from ethyl alcohol, had m. p. 108° (Found: C, 65·9; H, 4·45; N, 8·6; Cl, 11·15. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6; Cl, 10·9%). This ester was also prepared through the acid chloride by dissolving the acid in dry chloroform, adding a slight excess of thionyl chloride, allowing to stand for 4 hours and then refluxing for one hour. On removing the chloroform a crystalline product, evidently the hydrochloride of the acid chloride remained, which, on treatment with warm ethyl alcohol, was immediately converted into the ethyl ester identical with that obtained by direct esterification. The ester was soluble in dilute acid and insoluble in dilute alkali.

5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine.—4-Chloro-(6′-quinolyl)anthranilic acid (7 g.) was refluxed with phosphoryl chloride (30 c.c.) in an oil bath at 150° for 4 hours. The excess phosphoryl chloride was distilled away under reduced pressure and the brown residue, after trituration with cold 20% sodium hydroxide, yielded *5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine* as a pale brown crystalline solid. It was important to add the powdered residue in small quantities to the sodium hydroxide solution in such a way that neutralisation of any acid took place immediately and without local heating; otherwise a considerable proportion of the dichloro-compound might be hydrolysed to the acridone. The dichloropyridoacridine was separated, washed till neutral and dried (4·9 g.). Three crystallisations from dry benzene yielded pale yellow needles, m. p. 219° (Found: C, 64·1; H, 2·8; N, 9·5; Cl, 23·8. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·75%). 5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine exhibited a green fluorescence in alcohol and benzene solutions; it was soluble in dilute acid and insoluble in alkali. When heated at 100° for 2 hours with 2N-NaOH it was unchanged. It was very readily converted on treatment with hot dilute acid into 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone and even prolonged boiling with neutral solvents such as alcohol and benzene containing traces of water caused hydrolysis of the 5-chlorine atom. For this reason the benzene used for recrystallisation of this and analogous 5-chloropyridoacridines described below had to be carefully dried and, even with such precautions, it was difficult to obtain these chloropyridoacridines pure enough for analysis.

8-Chloro-3 : 4 : 2′ : 3′-pyridoacridone.—5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) was heated at 100° with N-HCl (10 c.c.) for 2 hours, a yellow crystalline compound, m. p. 386—387°, separating. It was the hydrochloride of 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone since, when treated with dilute alkali, a pale brown solid, m. p. 295—296°, was produced. When crystallised from ethyl alcohol, *8-chloro-3 : 4 : 2′ : 3′-pyridoacridone* separated in fine needles, m. p. 298° (Found: N, 9·6. $C_{16}H_9ON_2Cl$ requires N, 10·0%). The chloropyridoacridone hydrochloride was also obtained by refluxing 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine with ethyl alcohol for one hour. The yellow crystalline solid, treated with dilute alkali, yielded 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone, m. p. 296°. 8-Chloro-3 : 4 : 2′ : 3′-pyridoacridone was very soluble in concentrated sulphuric acid in which it exhibited a marked green fluorescence. The solution in alcohol had a slight green fluorescence. The compound was only very slightly soluble in dilute mineral acid and was insoluble in dilute acetic acid and dilute alkali.

8-Chloro-5-phenoxy-3 : 4 : 2′ : 3′-pyridoacridine.—Carefully dried 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (6 g.) was added to freshly distilled molten phenol (24 g.), previously heated under reduced pressure for an hour at 100°, and the solution heated at 160° for 4 hours. The phenol mixture was poured into 2N-NaOH (150 c.c.) and the brown solid separated. After drying, this was treated with hot dry ligroin which left a small quantity of chloropyridoacridone undissolved. On cooling the *8-chloro-5-phenoxy-3 : 4 : 2′ : 3′-pyridoacridine* separated in pale orange needles, m. p. 218° (Found: C, 74·0; H, 3·55; N, 8·05. $C_{22}H_{13}ON_2Cl$ requires C, 74·1; H, 3·65; N, 7·9%). Its solutions in organic solvents and in dilute acid exhibited green fluorescence. When heated at 100° for 2 hours with dilute sodium hydroxide it remained unchanged. Like the dichloro-pyridoacridine, it was hydrolysed to the acridone when heated with dilute acid.

8-Chloro-5-(β-diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine.—To redistilled phenol (4 g., dried in a vacuum at 100° for 2 hours) β-diethylaminoethylamine (0·3 g.) was added, and the mixture dried as before for another hour. If these precautions to remove traces of water were not taken a large proportion of the dichloropyridoacridine was converted to the chloropyridoacridone and the yield of the desired base correspondingly reduced. 5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g., dried in the desiccator) was introduced and the dark red-brown mixture heated at 100° under reflux for 2 hours; it then showed the presence of chlorine ions. The cooled phenol mixture was poured into 2N-NaOH (30 c.c.) and the brown precipitate extracted with ether. The base was purified from admixed chloropyridoacridone by shaking the ethereal solution with 5% acetic acid, reprecipitating with ammonia and re-extracting with ether. This ethereal extract was dried with potassium carbonate and, after removing the ether by distillation, the residual red-brown oily solid was heated at 100° under reduced pressure to remove excess ethylamine base. The residual *8-chloro-5-(β-diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine* was dissolved in hot dry ligroin and, on cooling, separated in pale yellow micro-needles. These were crystallised twice from dry ligroin and had m. p. 127° (Found: C, 68·6; H, 6·05; Cl, 9·15. $C_{22}H_{23}N_4Cl,\frac{1}{2}H_2O$ requires C, 68·9; H, 6·1; Cl, 9·3%). The base exhibited a marked green fluorescence in alcohol and in ether. It was soluble in dilute acids with the formation of the corresponding salts which exhibited a green fluorescence in solution. Unless otherwise stated all the succeeding bases had similar properties.

8-Chloro-5-(γ-diethylaminopropyl)amino-3 : 4 : 2′ : 3′-pyridoacridine was prepared from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and γ-diethylaminopropylamine (0·3 g.) in phenol (4 g.) as described above. The base (0·4 g.) separated from hot ligroin in yellow needles, m. p. 119·5—120° (Found: N, 13·8. $C_{23}H_{25}N_4Cl,H_2O$ requires N, 13·65%). The base exhibited a faint blue fluorescence in very dilute alcoholic, ethereal and acid solutions.

8-Chloro-5-(δ-diethylamino-α-methylbutyl)amino-3 : 4 : 2′ : 3′-pyridoacridine was prepared from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and 2-amino-5-diethylaminopentane (0·35 g.) in phenol (4 g.) under anhydrous conditions. This base (0·47 g.) could not be obtained crystalline; it yielded a solid acetate, m. p. 76—78°. The *picrate*, obtained by adding an ethereal solution of picric acid to a solution of the base in ether, crystallised from ethyl alcohol in yellow needles, m. p. 216° (Found: C, 46·3; H, 3·75; N, 16·35; Cl, 3·85. $C_{25}H_{29}N_4Cl,3C_6H_3O_7N_3$ requires C, 46·6; H, 3·4; N, 16·4; Cl, 3·2%).

8-Chloro-5-(γ-dimethylaminopropyl)amino-3 : 4 : 2′ : 3′-pyridoacridine, from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and γ-dimethylaminopropylamine (0·25 g.) in phenol (4 g.), crystallised from ligroin in yellow needles (0·4 g.), m. p. 127° (Found: C, 68·95; H, 6·0; N, 15·05. $C_{21}H_{21}N_4Cl$ requires C, 69·1; H, 5·8; N, 15·4%).

8-Chloro-5-(γ-butylaminopropyl)amino-3 : 4 : 2′ : 3′-pyridoacridine, from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and γ-butylaminopropylamine (0·3 g.) in phenol (4 g.), crystallised from ligroin in yellow needles (0·43 g.), m. p. 78° (Found: C, 67·0; H, 6·1; N, 13·3. $C_{23}H_{25}N_4Cl,H_2O$ requires C, 67·2; H, 6·6; N, 13·65%).

8-Chloro-5-(δ-diethylaminobutyl)amino-3 : 4 : 2′ : 3′-pyridoacridine, from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and δ-diethylaminobutylamine (0·35 g.) in phenol (4 g.). The base (0·45 g.) was not obtained crystalline, but yielded a *picrate*, which crystallised from ethyl alcohol in small yellow needles, m. p. 168° (Found: C, 45·05; H, 4·05; N, 16·15. $C_{24}H_{27}N_4Cl,3C_6H_3O_7N_3,H_2O$ requires C, 45·3; H, 3·4; N, 16·4%). The base yielded a *3 : 5-dinitrobenzoate* which crystallised from ethanol in small pale yellow needles, m. p. 233° (Found: C, 53·8; H, 4·2; N, 13·6. $C_{34}H_{27}N_4Cl.2C_7H_4O_6N_2,H_2O$ requires C, 53·8; H, 4·4; N, 13·2%). This dinitrobenzoate was conveniently used for purifying the base.

(6′-Quinolyl)anthranilic Acid.—Potassium *o*-chlorobenzoate (19·5 g.), 6-aminoquinoline (14·4 g.), amyl alcohol (30 c.c.) and copper bronze (0·1 g.) were refluxed at 150° for 6 hours. The brown solid was separated, washed with cold acetone and dissolved in a large volume of hot dilute ammonia. When the hot filtered solution was carefully acidified with acetic acid the (6′-quinolyl)anthranilic acid (16·2 g.) separated as a yellow solid. The acid crystallised from ethyl alcohol in pale yellow needles, m. p. 246—247°, and closely resembled 4-chloro-(6′-quinolyl)anthranilic acid in general properties. The ethyl ester was prepared by refluxing the acid (3 g.) with a mixture of ethanol (20 c.c.) and concentrated sulphuric acid (10 c.c.). The alcoholic solution was poured into ice-water, the orange solution filtered and the filtrate basified with ammonia; the ester separated as a pale yellow crystalline solid (2·2 g.). *Ethyl (6′-quinolyl)anthranilate* crystallised from ethanol in pale yellow needles, m. p. 92·5° (Found: C, 73·5; H, 5·2; N, 9·75. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). The ester was soluble in dilute acid and insoluble in dilute alkali.

5-Chloro-3 : 4 : 2′ : 3′-pyridoacridine.—(6′-Quinolyl)anthranilic acid (6 g.) was refluxed with phosphoryl chloride (30 c.c.) at 150° for 4 hours. The excess phosphoryl chloride was distilled under reduced pressure from the dark brown solution and the brown residue triturated with cold 20% sodium hydroxide. The same precautions to prevent hydrolysis to the acridone were observed as for 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine. The *5-chloro-3 : 4 : 2′ : 3′-pyridoacridine* (4·6 g.) was separated, washed until neutral and recrystallised from dry benzene in pale brown-yellow needles, m. p. 181·5—182° (Found: C, 70·9; H, 3·5; N, 10·5; Cl, 13·4. $C_{16}H_9N_2Cl,\frac{1}{2}H_2O$ requires C, 71·4; H, 3·5; N, 10·4; Cl, 13·2%). 5-Chloro-3 : 4 : 2′ : 3′-pyridoacridine is soluble in alcohol, benzene and cold dilute acid. When heated at 100° for 2 hours with 2N-NaOH it did not dissolve and remained unchanged. It was very unstable to hot acids or even neutral solvents containing water, the acridone being formed.

3 : 4 : 2′ : 3′-Pyridoacridone.—When 5-chloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) was heated at 100° with N-HCl (10 c.c.) for 2 hours a pale yellow crystalline compound separated which did not melt below 360°. It was evidently a hydrochloride for when treated with dilute alkali a light brown solid (0·84 g.), free from chlorine, was obtained which melted at 357°. The *3 : 4 : 2′ : 3′-pyridoacridone*, crystallised from ethanol, had m. p. 360° (Found: N, 10·5. $C_{16}H_{10}ON_2,H_2O$ requires N, 10·6%). This compound was also obtained directly by heating (6′-quinolyl)-anthranilic acid (2 g.) with concentrated sulphuric acid (10 c.c.) at 100° for 4 hours. The acid solution, having a marked green fluorescence, was cooled and poured into ice-water. When the filtered dark orange solution was made alkaline with sodium hydroxide 3 : 4 : 2′ : 3′-pyridoacridone, m. p. 358°, separated. 3 : 4 : 2′ : 3′-Pyridoacridone is highly soluble in conc. sulphuric acid, sparingly soluble in dilute acid and insoluble in dilute alkali.

5-(β-Diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine was prepared by condensing 5-chloro-3 : 4 : 2′ : 3′-pyridoacridine (0·5 g.) with β-diethylaminoethylamine (0·3 g.) in dry phenol (4 g.) at 100°, the usual care being taken to remove water. The product was isolated as in previous cases. The base (0·41 g.) crystallised from ligroin in pale yellow needles, m. p. 92° (Found: C, 76·45; H, 7·4; N, 16·1. $C_{22}H_{24}N_4$ requires C, 76·7; H, 7·0; N, 16·3%).

5-(δ-Diethylamino-α-methylbutyl)amino-3 : 4 : 2′ : 3′-pyridoacridine, prepared from 5-chloro-3 : 4 : 2′ : 3′-pyridoacridine (0·5 g.) and 2-amino-5-diethylaminopentane (0·35 g.) in dry phenol (4 g.), was isolated as usual. The non-crystalline base (0·46 g.) formed a *picrate* which crystallised from ethanol in bright yellow needles, m. p. 121° (Found: C, 48·5; H, 4·4; N, 15·9. $C_{25}H_{30}N_4,2C_6H_3O_7N_3,3H_2O$ requires C, 49·5; H, 4·7; N, 15·6%).

(8′-Quinolyl)anthranilic Acid.—Potassium *o*-chlorobenzoate (9·7 g.) 8-aminoquinoline (7·2 g.), amyl alcohol (15 c.c.) and copper bronze (0·1 g.) were refluxed together in an oil bath at 150° for 6 hours. The dark brown solid was separated, washed with cold acetone and dissolved in a large volume of hot dilute ammonia. The solution was filtered and the yellow filtrate acidified with acetic acid. (8′-Quinolyl)anthranilic acid separated as a yellow precipitate (8·8 g.). It crystallised from ethanol in pale yellow needles, m. p. 243—244°. (8′-Quinolyl)anthranilic acid is soluble in pyridine and dilute alkali. From more concentrated alkali, a relatively insoluble sodium or potassium salt tends to separate. It is insoluble in dilute acid. The *methyl ester* was prepared by refluxing the acid (3 g.) with methanol (20 c.c.) and concentrated sulphuric acid (8 c.c.) for 2 hours. The solution was poured into ice-water, the orange solution filtered, the filtrate basified with ammonia and the pale yellow solid (2·7 g.) collected. The ester, crystallised from ethyl alcohol, had m. p. 142—143° (Found: C, 74·1; H, 4·8; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%). The ester is soluble in dilute acid and insoluble in dilute alkali.

5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine.—(8′-Quinolyl)anthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) were refluxed at 140° for 4 hours. The phosphoryl chloride was removed by distillation under reduced pressure and the solid residue triturated with cold 20% sodium hydroxide solution, the usual precautions being taken to avoid hydrolysis to the acridone. The brown-yellow solid (4·4 g.) was filtered off, washed until neutral and crystallised from dry benzene. *5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine* separated in small pale yellow needles, m. p. 165° (Found: C, 68·0; H, 3·7; Cl, 12·3. $C_{16}H_9N_2Cl,H_2O$ requires C, 68·0; H, 3·9; Cl, 12·6%). It is soluble in cold dilute acid and insoluble in dilute alkali. When heated at 100° with 2N-NaOH for 2 hours it remained unaltered. Like the chloropyridoacridines of the previous series, it is very unstable when heated with acids or even neutral solvents containing moisture, the acridone being produced.

1 : 2 : 2′ : 3′-Pyridoacridone.—When 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) was heated with N-HCl (8 c.c.) for 2 hours an orange yellow solid (0·4 g.), m. p. 273°, separated. This was the base *1 : 2 : 2′ : 3′-pyridoacridone* and not the hydrochloride, as might have been expected. Crystallised from ethanol, it had m. p. 275—276° (Found: C, 77·8; H, 4·4; N, 11·0. $C_{16}H_{10}ON_2$ requires C, 78·0; H, 4·1; N, 11·4%). 1 : 2 : 2′ : 3′-Pyridoacridone was also prepared by heating (8′-quinolyl)anthranilic acid (2 g.) with concentrated sulphuric acid (8 c.c.) for 4 hours at 100°

The solution was poured into ice-water, the filtered solution made alkaline with sodium hydroxide and the greenish-yellow solid (1·2 g.), m. p. 273°, separated. It did not depress the m. p. of the 1 : 2 : 2′ : 3′-pyridoacridone from the previous experiment. 1 : 2 : 2′ : 3′-Pyridoacridone is very soluble in conc. sulphuric acid in which it exhibits a marked green fluorescence, sparingly soluble in dilute acid and insoluble in dilute alkali.

4-Chloro-(8′-quinolyl)anthranilic acid, prepared from 8-aminoquinoline (28·8 g.), potassium 2 : 4-dichlorobenzoate (45·8 g.), amyl alcohol (60 c.c.) and copper bronze (0·5 g.) refluxed at 150° for 6 hours, was isolated in the usual way. Crystallised from ethyl alcohol, it was obtained as small pale yellow needles, m. p. 239—240°. It closely resembled (8′-quinolyl)anthranilic acid in general properties. The *ethyl ester* was prepared by refluxing the acid (5 g.) with ethanol (25 c.c.) and concentrated sulphuric acid (10 c.c.); it was isolated in the usual manner as a yellow oil which was extracted with ether. After drying the extract, the ether was removed by distillation; the oily residue solidified when gently warmed with sodium bicarbonate solution. Crystallised from ethanol, the ester formed pale yellow monoclinic crystals, m. p. 103° (Found: C, 66·1; H, 4·7; N, 8·65; Cl, 11·5. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6; Cl, 10·9%). It is soluble in conc. mineral acid, slightly soluble in dilute acid, and insoluble in dilute alkali.

5 : 8-*Dichloro*-1 : 2 : 2′ : 3′-*pyridoacridine*, prepared by refluxing 4-chloro-(8′-quinolyl)anthranilic acid (8 g.) with phosphoryl chloride (30 c.c.) at 150° for 4 hours, was isolated as described for the monochloropyridoacridine. Crystallised from dry benzene it had m. p. 238° (Found: C, 63·5; H, 2·9; N, 9·2; Cl, 23·7. $C_{18}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·75%). The properties of this compound closely resembled those of 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine.

8-*Chloro*-1 : 2 : 2′ : 3′-*pyridoacridone*, prepared by heating 5 : 8-dichloro-1 : 2 : 2′ : 3′-pyridoacridine (1 g.) with N-HCl (10 c.c.) at 100° for 2 hours, crystallised from ethanol in small yellow needles, m. p. 311° (Found: C, 67·35; H, 3·4; N, 10·15; Cl, 12·65. $C_{18}H_9ON_2Cl$ requires C, 68·4; H, 3·2; N, 10·0; Cl, 12·65%). It closely resembled 1 : 2 : 2′ : 3′-pyridoacridone in general properties.

(6′-Methoxy-8′-quinolyl)anthranilic acid, prepared from 8-amino-6-methoxyquinoline (17·4 g.), potassium *o*-chlorobenzoate (19·5 g.), amyl alcohol (30 c.c.) and copper bronze (0·2 g.) refluxed at 150° for 4 hours, was isolated as described for (8′-quinolyl)-anthranilic acid. Crystallised from ethanol, the acid (18·8 g.) separated in yellow needles, m. p. 201°. It closely resembled (8′-quinolyl)anthranilic acid in general properties. The *ethyl ester* was prepared by refluxing the acid (5 g.) with ethyl alcohol (25 c.c.) and sulphuric acid (10 c.c.) and pouring into ice-water. The yellow crystalline ester was crystallised from ethanol; it had m. p. 91° (Found: C, 70·6; H, 5·95; N, 8·85. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). Its properties resembled those of ethyl (8′-quinolyl)anthranilate.

5-*Chloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine*, prepared from (6′-methoxy-8′-quinolyl)anthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) refluxed at 150° for 4 hours, was isolated as described for 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine. It crystallised from dry benzene in pale yellow needles (4·8 g.), m. p. 169° (Found: C, 67·7; H, 4·2; N, 9·85; Cl, 11·9. $C_{17}H_{11}ON_2Cl,\frac{1}{2}H_2O$ requires C, 67·2; H, 3·95; N, 9·2; Cl, 11·7%). It closely resembled 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine in general properties.

4-*Methoxy*-1 : 2 : 2′ : 3′-*pyridoacridone*.—When 5-chloro-4-methoxy-1 : 2 : 2′ : 3-pyridoacridine (1 g.) and N-HCl (10 c.c.) were heated at 100° for 2 hours the orange hydrochloride (m. p. 298—299°) separated; on making the mixture alkaline the *acridone* was obtained. After crystallisation from ethanol the canary yellow needles had m. p. 245·5° (Found: C, 72·9; H, 4·6; N, 10·3. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·35; N, 10·15%). The properties of this compound closely resembled those of 1 : 2 : 2′ : 3′-pyridoacridone.

4-Chloro-(6′-methoxy-8′-quinolyl)anthranilic acid was prepared by refluxing potassium 2 : 4-dichlorobenzoate (22·9 g.), 8-amino-6-methoxyquinoline (17·4 g.), amyl alcohol (30 c.c.) and copper bronze (0·2 g.) at 150° for 4 hours. The purification of this acid was carried out similarly to that of (8′-quinolyl)-anthranilic acid. It crystallised from ethanol in small yellow needles (18·8 g.), m. p. 258—259°. It resembled (8′-quinolyl)anthranilic acid in general properties. The *ethyl ester* was produced by refluxing the acid (5 g.) with ethyl alcohol (25 c.c.) and sulphuric acid (10 c.c.) and isolated in the usual manner. The yellow solid (4·1 g.) was crystallised from ethanol and obtained in pale yellow needles, m. p. 111° (Found: C, 63·35; H, 4·85; N, 8·1; Cl, 10·0. $C_{19}H_{17}O_3N_2Cl$ requires C, 63·95; H, 4·8; N, 7·85; Cl, 9·95%). The ester closely resembled ethyl (8′-quinolyl)anthranilate in general properties.

5 : 8-*Dichloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyrodoacridine* was obtained by refluxing 4-chloro-(6′-methoxy-8′-quinolyl)-anthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) at 150° for 4 hours and isolated as described for 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine. It crystallised from dry benzene in pale brown-yellow needles (4·5 g.), m. p. 196—197° (Found: N, 8·8. $C_{17}H_{10}ON_2Cl_2$ requires N, 8·5%). The properties of this compound closely resembled those of 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine.

8-*Chloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridone*, obtained from 5 : 8-dichloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (1 g.) and N-HCl (10 c.c.) at 100°, separated as the hydrochloride (m. p. 310—312°) for, when treated with alkali, the acridone was obtained. The acridone crystallised from alcohol in yellow needles, m. p. 257—258° (Found: C, 64·3; H, 3·55; N, 9·25; Cl, 11·65. $C_{17}H_{11}O_2N_2Cl,\frac{1}{2}H_2O$ requires C, 64·8; H, 3·65; N, 8·9; Cl, 11·3%). It resembled 1 : 2 : 2′ : 3′-pyridoacridone in general properties.

The following bases were prepared by heating the appropriate 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine and diethylaminoalkylamine in dry phenol for 2 hours at 100° with the same precautions as described for the preparation of 8-chloro-5-(β-diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine (p. 152). The bases were separated from admixed pyridoacridone by extracting the ethereal solution with dilute acetic acid. The base precipitated from the acid solution by the addition of ammonia was extracted with ether and, after drying, the ether was removed by distillation.

5-(β-Diethylaminoethyl)amino-1 : 2 : 2′ : 3′-pyridoacridine was prepared from 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) and β-diethylaminoethylamine (0·3 g.) in phenol (4 g.). The non-crystalline base yielded a crystalline *picrate* which crystallised from ethanol in small bright yellow needles, m. p. 196° (Found: C, 49·8; H, 4·15; N, 17·4. $C_{22}H_{24}N_4,2C_6H_3O_7N_3,H_2O$ requires C, 49·8; H, 3·9; N, 17·1%).

5-(δ-Diethylamino-α-methylbutyl)amino-1 : 2 : 2′ : 3′-pyridoacridine was obtained from 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in dry phenol (4 g.). The non-crystalline base (0·45 g.) yielded a *picrate* which crystallised from ethanol in bright yellow needles, m. p. 198° (Found: C, 52·35; H, 4·35; N, 16·7. $C_{28}H_{30}N_4,2C_6H_3O_7N_3$ requires C, 52·6; H, 4·3; N, 16·6%).

8-*Chloro*-5-(β-*diethylaminoethyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* was prepared from 5 : 8-dichloro-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and β-diethylaminoethylamine (0·3 g.) in phenol (4 g.). The base (0·42 g.) crystallised from ligroin in small pale yellow needles, m. p. 131° (Found: C, 69·8; H, 6·15. $C_{22}H_{23}N_4Cl$ requires C, 69·75; H, 6·1%). It exhibited a marked blue fluorescence, persisting to high dilutions, in alcoholic and ethereal solutions. Its solution in dilute acids exhibited only a very faint blue fluorescence.

8-*Chloro*-5-(δ-*diethylamino*-α-*methylbutyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* (0·48 g.), obtained from 5 : 8-dichloro-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in phenol (4 g.), crystallised from dry ligroin in pale yellow needles, m. p. 118° (Found: C, 71·8; H, 6·85; Cl, 8·0. $C_{25}H_{29}N_4Cl$ requires C, 71·35; H, 6·9; Cl, 8·4%). The base yielded a crystalline *hydrobromide*, m. p. 282° (Found: C, 42·85; H, 5·3; N, 7·6; Ag halides from 1 mg. of compound, 0·999 mg. $C_{25}H_{29}N_4Cl,3HBr,2H_2O$ requires C, 42·9; H, 5·2; N, 8·0%; Ag halides, 1·012 mg.). This hydrobromide was very soluble in water and exhibited a marked green fluorescence even at high dilution.

5-(β-Diethylaminoethyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine was obtained from 5-chloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and β-diethylaminoethylamine (0·3 g.) in dry phenol (4 g.). The non-crystalline base (0·46 g.) yielded a *picrate* which crystallised from alcohol and had m. p. 118° (Found: C, 47·25; H, 4·45. $C_{23}H_{26}ON_4,2C_6H_3O_7N_3,3H_2O$ requires C, 47·4; H, 4·3%).

5-(δ-Diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, obtained from 5-chloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in phenol (4 g.), did not crystallise but yielded a crystalline *picrate* which crystallised from alcohol in small bright yellow needles, m. p. 201° (Found: C, 52·2; H, 4·4; N, 16·15. $C_{26}H_{32}ON_4,2C_6H_3O_7N_3$ requires C, 52·2; H, 4·35; N, 16·0%).

8-*Chloro*-5-(β-*diethylaminoethyl*)*amino*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* (0·42 g.), obtained from 5 : 8-dichloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·65 g.) and β-diethylaminoethylamine (0·3 g.) in phenol (4 g.), crystallised from dry ligroin in small pale yellow needles, m. p. 152° (Found: C, 68·2; H, 6·15; Cl, 8·75. $C_{23}H_{25}ON_4Cl$ requires C, 67·6; H, 6·1; Cl, 8·7%). In alcohol and in ether it exhibited a marked blue fluorescence persisting at high dilution. The fluorescence almost entirely disappeared when the solutions were made acid.

8-Chloro-5-(δ-diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, obtained from 5 : 8-dichloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·65 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in phenol (4 g.), did not crystallise from ligroin but yielded a crystalline *picrate* which crystallised from alcohol in orange-yellow needles (1·1 g.), m. p. 158—159° (Found: C, 50·4; H, 4·3; N, 15·35; Cl, 4·3. $C_{26}H_{31}ON_4Cl,2C_6H_3O_7N_3$ requires C, 50·2; H, 4·1; N, 15·4; Cl, 3·9%).

We are indebted to Imperial Chemical Industries Limited for facilities in connection with the above work, and thank their analytical department for most of the microanalyses.

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43. *Attempts to find New Antimalarials. Part XXIV. Derivatives of* o-*Phenanthroline* (7 : 8 : 3′ : 2′-*pyridoquinoline*).

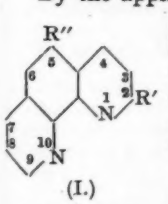
By BARBARA E. HALCROW and WILLIAM O. KERMACK.

o-*Phenanthroline methiodide*, oxidised by alkaline ferricyanide, yields 1-*methyl*-2-o-*phenanthrolone*. Hence 2-*chloro*-o-*phenanthroline*, from which *o*-phenanthroline compounds carrying various basic substituents in the 2-position have been prepared. 5-Bromo-*o*-phenanthroline has been prepared from 5-bromo-8-aminoquinoline, but, on treatment with ammonia, 5-amino-*o*-phenanthroline could not be isolated.

That the nitro group in the nitro-*o*-phenanthroline, obtained by nitrating *o*-phenanthroline, is in the 5 position is proved by the synthesis of the same nitro compound from 5-nitro-8-aminoquinoline.

VARIOUS derivatives of *m*- and *p*-phenanthrolines carrying basic side-chains of the type present in mepacrine (atebrin) are described in the literature, and in a recent communication Burger, Bass, and Fredericksen (*J. Org. Chem.*, 1944, **9**, 373) have described derivatives of 4-methyl-*o*-phenanthroline carrying a basic side-chain in the 2-position. The following convenient route to *o*-phenanthroline derivatives carrying the basic side-chain in the 2-position, but with no methyl group in the 4-position, gives good results.

By the application of the Skraup reaction to *o*-phenylenediamine under the conditions described in E.P. 394,416, reasonable yields of *o*-phenanthroline were obtained with much less labour than is involved in the methods of Hieber (*Ber.*, 1928, **61**, 2150) and of Tartarini and Samaja (*Annali Chim. Appl.*, 1933, **23**, 351). The *monomethiodide* of *o*-phenanthroline when oxidised with alkaline ferricyanide yields 1-*methyl*-2-o-*phenanthrolone*. Treatment of this compound by a mixture of phosphorus oxychloride and phosphorus pentachloride slowly converts it into the desired 2-*chloro*-o-*phenanthroline* (I; R′ = Cl, R″ = H).



(I.)

As expected, the chlorine atom of 2-chloro-*o*-phenanthroline reacts readily with suitable primary and secondary amines. Thus, with aniline it yields 2-*anilino*-o-*phenanthroline* and with piperidine, 2-piperidino-*o*-phenanthroline (which was characterised as its *picrate*). With the appropriate diethylaminoalkylamines the following bases were obtained: 2-diethylaminoethylamino-*o*-phenanthroline, 2-diethylaminopropylamino-*o*-phenanthroline, and 2-(δ-diethylamino-α-methylbutylamino)-*o*-phenanthroline. None of these was obtained crystalline, or gave a satisfactory hydrochloride or hydrobromide. The picrates did not crystallise well, but the *salts* with 3 : 5-dinitrobenzoic acid were well defined and relatively easily purified.

5-Bromo-*o*-phenanthroline (I; R′ = H, R″ = Br) has been synthesised from 5-bromo-8-aminoquinoline by means of a modified Skraup reaction. This compound has recently been prepared by Richter and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 396) from 6-bromo-8-aminoquinoline. The synthesised compound, containing half a molecule of water, has m. p. 113—115°, slightly lower than that (119°) given by these authors for the anhydrous material; there is no reason to believe that the two compounds are not identical. When 5-bromo-*o*-phenanthroline is heated with ammonia, phenol, and a little copper sulphate under the conditions described by Haworth and Sykes (*J.*, 1944, 311) bromide ions are liberated, but none of the expected 5-amino-*o*-phenanthroline (I; R′ = H, R″ = NH_2) could be isolated. The only products which could be separated were *o*-phenanthroline, a compound, probably 5-*phenoxy*-o-*phenanthroline* (I; R′ = H, R″ = OPh), and some intractable tar; as the crude product gives a positive diazo reaction, the amino-derivative is probably present in small amount. It appears that, at the high temperature employed, some molecules of the 5-bromo-*o*-phenanthroline are reduced whilst others are decomposed or polymerised.

A nitro-*o*-phenanthroline, m. p. 202°, has been obtained by Hammett, Walden, and Edmonds (*J. Amer.*

Chem. Soc., 1934, **56**, 1093) by nitrating *o*-phenanthroline. That the nitro group is in the 5-position is now proved by the synthesis of the identical nitro-*o*-phenanthroline from 5-nitro-8-aminoquinoline by the Skraup reaction. Attempts to synthesise 5-nitro-*o*-phenanthroline directly from 4-nitro-*o*-phenylenediamine by a double Skraup reaction have so far not been successful. Haworth and Sykes (*loc. cit.*) state that they could not isolate the *m*- and *p*-derivatives by this method from 4-nitro-*m*-phenylenediamine and 2-nitro-*p*-phenylenediamine.

Experimental.

Preparation of o-*Phenanthroline.*—A mixture of *o*-phenylenediamine (40 g.), sulphuric acid (880 c.c., 69%), glycerol (216 g.), arsenic acid solution (200 c.c., 80%, *d* 1·9) and water (24 c.c.) was refluxed for 2—3 hours. The end of the reaction was indicated by voluminous frothing. The black liquid diluted with an equal volume of water was basified with ammonia. The tarry material was separated by filtration and the filtrate extracted with benzene. The tar was refluxed with benzene until the extracts were colourless. The benzene extracts were combined and the benzene removed. The crude material (30 g., 45%) was crystallised from benzene and the product had m. p. 108—112°.

o-*Phenanthroline Methiodide.*—Methyl iodide (5 c.c.) was added to a solution of *o*-phenanthroline (6 g.) in nitrobenzene (150 c.c.) and the mixture kept at 37° for 24 hours. The long yellow crystalline plates were separated. More methyl iodide (2·5 c.c.) was added to the filtrate and after 24 hours a further crop of crystals separated. After washing with benzene the crystals (8·5 g.) were crystallised from alcohol, m. p. 210—213° (Found: C, 48·8; H, 3·8; I, 40·2. $C_{13}H_8N_2$,MeI requires C, 48·4; H, 3·4; I, 39·4%). o-*Phenanthroline methiodide* was readily soluble in water and from the solution the metho-hydroxide was precipitated by concentrated but not by dilute sodium hydroxide or ammonia. The compound gave no colour with ferrous sulphate solution.

1-*Methyl*-2-o-*phenanthrolone.*—To a cold saturated aqueous solution of potassium ferricyanide (7·3 g.) were added alternately a little at a time saturated solutions of sodium hydroxide and *o*-phenanthroline methiodide (3 g.), excess sodium hydroxide being added until no further precipitation took place. The yellow precipitate and the pale pink residual solid, obtained by evaporating the filtrate to dryness, were refluxed with benzene to give a red extract with green fluorescence. The brown solid, obtained on removal of the benzene, crystallised from water and from benzene as rectangular plates (1·5 g.), m. p. 123—124°. The compound retained the solvent tenaciously, as shown by the analytical results obtained on samples dried at 78° under reduced pressure. (Sample, crystallised from water. Found: C, 72·6; H, 5·4. $C_{13}H_{10}ON_2$ requires C, 74·3; H, 4·8. $C_{13}H_{10}ON_2,\frac{1}{4}H_2O$ requires C, 72·7; H, 4·9%. Sample, crystallised from benzene. Found: C, 75·5; H, 5·1. $C_{13}H_{10}ON_2,\frac{1}{4}C_6H_6$ requires C, 75·8; H, 5·0%). The compound was insoluble in cold dilute sodium hydroxide, but soluble in dilute hydrochloric acid. It gave no colour with ferrous sulphate solution.

2-*Chloro*-o-*phenanthroline.*—1-Methyl-2-*o*-phenanthrolone (6 g.), phosphorus pentachloride (7·2 g.), and phosphorus oxychloride (54 c.c.) were refluxed for 8 hours. After removal of excess phosphorus oxychloride by distillation under reduced pressure, iced water was added and the solution basified with ammonia. The pale brown precipitate crystallised from hot water as colourless needles (5 g.), m. p. 129—130° (Found: Cl, 17·1. $C_{13}H_7N_2Cl$ requires Cl, 16·6%). It was soluble in dilute hydrochloric acid, insoluble in dilute sodium hydroxide, and dissolved in ferrous sulphate solution giving a deep yellow colour.

2-*Piperidino*-o-*phenanthroline.*—2-Chloro-*o*-phenanthroline (1 g.) and piperidine (0·5 g.) were heated at 100° for 2—3 hours. After excess piperidine had been removed under reduced pressure, the product was dissolved in 4N-acetic acid, basified with ammonia and extracted with ether. The ether solution was extracted with 4N-acetic acid and the acid layer separated off, basified with ammonia and again extracted with ether. The non-crystallisable orange oil, obtained on removal of the ether, was treated in alcoholic solution with picric acid and the orange *picrate* crystallised from alcohol as yellow rods, m. p. 213—217° (Found: C, 54·4; H, 4·2. $C_{17}H_{17}N_3,C_6H_3O_7N_3,H_2O$ requires C, 54·1; H, 4·3%).

2-*Anilino*-o-*phenanthroline.*—2-Chloro-*o*-phenanthroline (0·5 g.) and aniline (0·5 c.c.) were heated at 100° for 2 hours. The orange oily product was diluted with water and steam distilled. The pale brown solid left was crystallised from alcohol and then from benzene as colourless rods, m. p. 231—233° (Found: C, 79·4; H, 4·4. $C_{18}H_{13}N_3$ requires C, 79·7; H, 4·8%). It was insoluble in water and sodium hydroxide, soluble in hydrochloric acid and acetone. The compound was insoluble in cold ferrous sulphate solution, but on warming gave an orange solution.

2-*Diethylaminoethylamino*-o-*phenanthroline.*—2-Chloro-*o*-phenanthroline (3 g.) and diethylaminoethylamine (2·5 g.) were heated at 140—150° for 4 hours. Excess amine was removed under reduced pressure, and the thick residual oil was dissolved in 2N-acetic acid to form a red solution with green fluorescence. Basification with ammonia and extraction with ether gave an orange solution with faint green fluorescence. The base, a thick orange oil, was treated in alcoholic solution with 3 : 5-dinitrobenzoic acid. The *salt* quickly solidified and was recrystallised from alcohol as long yellow plates (5 g.), m. p. 190—192° (Found: C, 53·7; H, 4·4. $C_{18}H_{22}N_4,2C_7H_4O_6N_2$ requires C, 53·5; H, 4·2%).

2-Diethylaminopropylamino-*o*-phenanthroline was obtained from 2-chloro-*o*-phenanthroline (3 g.) and diethylaminopropylamine (2·5 g.) at 150—160° for 3—4 hours, the product being worked up as above. The base, a thick non-crystallisable orange oil, was converted into the *dinitrobenzoate* which crystallised from alcohol as long yellow plates (4 g.), m. p. 150—152° (Found: C, 53·8; H, 4·4. $C_{19}H_{24}N_4,2C_7H_4O_6N_2$ requires C, 54·1; H, 4·4%).

2-(δ-Diethylamino-α-methylbutylamino)-*o*-phenanthroline was obtained from 2-chloro-*o*-phenanthroline (3 g.) and δ-diethylamino-α-methylbutylamine (3·4 g.) at 160—170° for 5—6 hours. The *dinitrobenzoate* of the non-crystallisable red–brown oily base crystallised from alcohol as small yellow needles (5 g.), m. p. 157—158° (Found: C, 54·1; H, 4·9. $C_{21}H_{28}N_4,2C_7H_4O_6N_2,H_2O$ requires C, 54·0; H, 4·9%). These three dinitrobenzoates were closely similar in appearance and properties. They were slowly decomposed by dilute sodium hydroxide with liberation of the base, which could be extracted with ether.

Preparation of 5-*Bromo*-o-*phenanthroline.*—5-Bromo-8-aminoquinoline (Claus and Setzer, *J. pr. Chem.*, 1896, **53**, 405) (12 g.), sulphuric acid (56 c.c., 69%), glycerol (16 g.), arsenic acid solution (16 c.c., 80%, *d* 1·9), and water (6 c.c.) were refluxed for 2 hours, when the diazo test was negative. The acid product was diluted and basified with sodium hydroxide. The thin tar was separated and extracted by boiling in benzene. The dark red extract on removal of the benzene yielded a sticky brown solid which crystallised from ligroin as colourless needles (6 g.), m. p. 113—115° (Found, after drying at 78°, under reduced pressure: C, 54·1; H, 3·3. Calc. for $C_{12}H_7N_2Br,\frac{1}{2}H_2O$: C, 53·8; H, 3·0%). It was insoluble in dilute sodium hydroxide and soluble in dilute hydrochloric acid. The compound gave a deep red colour with ferrous sulphate solution in which it was soluble.

Attempt to prepare 5-*Amino*-o-*phenanthroline.*—5-Bromo-*o*-phenanthroline (3 g.), phenol (3 g.), concentrated aqueous ammonia (10 c.c.), and copper sulphate (0·3 g.) were heated in a sealed tube at 190° for 3 days. The thin black tar was separated and refluxed in benzene, yielding a dark brown residue and a reddish-brown extract which was shaken with dilute sodium hydroxide solution to remove phenol. On removal of the benzene the black residue was crystallised from ligroin and then from benzene. The crystalline compound (m. p. 96—112°) which separated on concentration of the benzene to small volume showed a negative diazo test, did not contain bromine and was crude *o*-phenanthroline as shown

by undepressed mixed m. p. On evaporating the benzene filtrate to dryness, an uncrystallisable orange-brown oil was obtained which gave a deep purple colour on diazotisation and coupling with β-naphthol. It was heated with acetic anhydride for an hour and the colourless solid, isolated in the usual way, crystallised from aqueous alcohol as colourless needles, m. p. 167—168°. This compound, after treatment with hot 5N-hydrochloric acid for 30 minutes, gave no diazo test, so that it did not appear to be the expected acetamido-derivative. It appeared to be *5-phenoxy-o-phenanthroline* (Found: C, 79·3; H, 4·5. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%). It is probable, as shown by the positive diazo test of the crude material, that some amino-*o*-phenanthroline was actually formed, but in too small quantity for successful isolation.

Preparation of 5-Nitro-o-phenanthroline.—(i) To a solution of *o*-phenanthroline (1 g.) in concentrated sulphuric acid (10 c.c.) a mixture of fuming nitric acid (2 c.c.) and concentrated sulphuric acid (2 c.c.) was added. After the mixture had been heated at 100° for 2 hours it was diluted with water and basified with sodium hydroxide. The light brown solid crystallised from alcohol as colourless needles, m. p. 199—201° (Found: C, 63·9; H, 2·7; N, 18·5. Calc. for $C_{12}H_7O_2N_3$: C, 64·0; H, 3·1; N, 18·7%).

(ii) 5-Nitro-8-aminoquinoline (Slater, *J.*, 1931, 1938) (1·3 g.), sulphuric acid (7 c.c., 69%), glycerol (2 g.), arsenic acid solution (2 c.c., 80%), and water (0·8 c.c.) were refluxed for 1—2 hours, when the diazo test was negative. The dark red–brown liquid was added to water, basified with sodium hydroxide, and extracted with ether. The yellow extract, on removal of the ether, yielded a sticky yellow solid which crystallised from ligroin in pale yellow needles (Found: C, 63·5; H, 3·2. Calc. for $C_{12}H_7O_2N_3$: C, 64·0; H, 3·1%). It had m. p. 202° and did not depress the m. p. of the product obtained in (i). The compound was insoluble in dilute sodium hydroxide and soluble in dilute hydrochloric acid. It dissolved in ferrous sulphate solution giving a red colour.

We thank the Medical Research Council for a grant to one of us (B. E. H.) which enabled this work to be carried out, and also for an expenses grant towards the cost of materials.

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44. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXVI. The Rôle of Steric Hindrance. (Section A) Introductory Remarks, and a Kinetic Study of the Reactions of Methyl, Ethyl,* n-*Propyl,* iso*Butyl, and* neo*Pentyl Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.*

By I. DOSTROVSKY and E. D. HUGHES.

These papers are concerned with the elucidation of the remarkable inactivity of the *neo*pentyl halides in certain substitution reactions (Whitmore, *et al.*). Our general precedure is to relate reactivity to mechanism and its determining factors, structure and experimental conditions, through a study of the rates of reaction of *neo*pentyl and other alkyl halides with various reagents under kinetically controlled conditions. In this paper we give the results of an examination of the bimolecular reaction (mechanism S_N2—see p. 158) of the halides, named in the title, with sodium ethoxide in dry ethyl alcohol. The rate sequence is found to be Me>Et>*n*-Pr>*iso*Bu≫*neo*pentyl, the relative rates (Et = 1) at 55° being: Me 18, Et 1, *n*-Pr 0·28, *iso*Bu 0·030, and *neo*pentyl $4·2 \times 10^{-6}$. The rate relationships for the first four members are fairly normal for the bimolecular mechanism, for which the rate is decreased by electron accession to the reaction centre, but the *neo*pentyl structure has obviously introduced an effect which is far larger than that to be expected on the basis of the electron release of its third methyl group. Evidence is adduced that this effect is of steric origin, but detailed discussion is deferred to the last of this group of papers (Part XXXII, this vol., p. 173).

Introduction to a Group of Papers.

THIS is the first of a small group of connected papers. It will be convenient to give here a very brief description of the nature of the problem undertaken, the method of attack adopted, and the main results obtained.

It was shown by Whitmore and his co-workers that the *neo*pentyl halides are extraordinarily inactive towards many reagents. Thus, except for the forming of a Grignard reagent and for a reaction with sodium, *neo*pentyl chloride did not, under the usual conditions, undergo any of the common reactions of the alkyl halides (Whitmore and Fleming, *J. Amer. Chem. Soc.*, **1933**, **55**, 4161; Whitmore, Popkin, Bernstein, and Wilkins, *ibid.*, 1941, **63**, 124). *neo*Pentyl iodide was, as might be expected, rather more reactive; nevertheless, under conditions which were completely effective for reaction in the case of the *n*-butyl halides, it showed little or no tendency to react with sodium ethoxide, potassium hydroxide or potassium cyanide, though it reacted fairly readily with aqueous silver nitrate. Moreover, when the iodide was caused to react with concentrated alcoholic potash at 180° it gave but a poor yield of ethyl *neo*pentyl ether, the major product consisting of *neo*pentane (Whitmore, Wittle, and Popkin, *ibid.*, **1939**, **61**, 1586). *neo*Pentyl alcohol also exhibits unusual stability with respect to the action of thionyl chloride and the halides of hydrogen and phosphorus (Whitmore and Rothrock, *ibid.*, **1932**, **54**, 3431). In this group of papers we record experimental data and theoretical discussions which contribute towards the elucidation of the properties of these interesting compounds.

In the absence of a certain knowledge of the mechanism of the reactions involved, evidence concerning the reactivity of organic compounds loses much of its significance. In previous papers in this series an attempt has been made, with the aid of kinetic data, to relate reactivity to mechanism. We have applied this method to some of the reactions of *neo*pentyl bromide. A satisfactory treatment of the problem involves a study of structural influences by means of a comparison with the corresponding reactions of certain other bromides *;

* Of the halides, the bromides were considered to be the most suitable as a basis for comparison because they are more reactive and less volatile than the chlorides and more free from side reactions than the iodides.

in particular, we have examined the effect of successive methyl substitution as illustrated in the series, CH_3Br, $CH_3{\cdot}CH_2Br$, $CH_3{\cdot}CH_2{\cdot}CH_2Br$, $(CH_3)_2CH{\cdot}CH_2Br$, $(CH_3)_3C{\cdot}CH_2Br$, thereby placing in a certain quantitative perspective some of the pecularities of *neo*pentyl compounds, to which Whitmore had drawn attention in qualitative terms.

The experimental work now described is concerned with the nucleophilic substitutions (S_N) of the halides indicated (cf. Hughes and Ingold, J., 1935, **244** and later papers). For reactions of this type, two distinct mechanisms are recognised, namely a one-stage, bimolecular mechanism (S_N2), involving a direct attack by the nucleophilic substituting agent, and a two-stage, unimolecular mechanism (S_N1), kinetically dependent on the ionisation of the alkyl halide, *e.g.*,

$$H_2O + R{-}Br \longrightarrow HO{-}R + \overset{+}{H} + \bar{B}r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N2)$$

$$\left.\begin{array}{rl} R{-}Br & \xrightarrow{\text{(slow)}} \overset{+}{R} + \bar{B}r \\ H_2O + \overset{+}{R} & \xrightarrow{\text{(fast)}} HO{-}R + \overset{+}{H} \end{array}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (S_N1)$$

While the main investigation refers to the behaviour of the halides in reactions which proceed by these or similar mechanisms, the results obtained enable certain conclusions to be reached with respect to the general chemistry of *neo*pentyl compounds.

Rate coefficients have been determined for the reactions of certain of the halides (always including *neo*pentyl bromide) with the following reagents: (1) sodium ethoxide in dry ethyl alcohol, (2) sodium iodide in acetone, (3) aqueous ethyl alcohol, (4) silver nitrate in aqueous ethyl alcohol,* (5) aqueous formic acid. On the basis of the results obtained, we shall show, *inter alia*, that *neo*pentyl bromide is singularly inert towards the bimolecular mechanism, but is moderately reactive under conditions favourable to the unimolecular mechanism. This circumstance makes it possible, under appropriate conditions, to observe the ionisation process in the case of *neo*pentyl bromide—an observation which is difficult to achieve with other primary halides. We shall adduce evidence for the view that the cause of the inactivity of the *neo*pentyl halides in bimolecular substitution is mainly of a steric character,† and that abnormal behaviour with regard to the ease of elimination of the halogen in these compounds is confined to reactions of the bimolecular type.

The Bimolecular Reaction with Sodium Ethoxide in Dry Ethyl Alcohol.

In this paper we deal with the reactions of the alkyl halides already named with sodium ethoxide in dry ethyl alcohol. All these substitutions are of the second order: they are evidently of the bimolecular type. Some of the necessary data relating to the first four members of the series were already available; the remainder, and all the data for *neo*pentyl bromide, were determined in the present work. The rate constants recorded in Table I refer solely to the substitution, a correction having been applied to the total rate constant to allow for the concurrent elimination, leading to olefin, which occurs in some cases. With *neo*pentyl bromide we found no evidence for the formation of *neo*pentane or the other products which Whitmore and his co-workers (*loc. cit.*) obtained from *neo*pentyl iodide and concentrated alcoholic potassium hydroxide at 180°. From the bromide, under the experimental conditions employed in our rate measurements (cf. experimental section), we obtained only ethyl *neo*pentyl ether. This may be regarded as auxiliary evidence of the bimolecular nature of this reaction, for in a later paper (this vol., p. **166**) we shall show that the unimolecular reaction of the same halide with aqueous ethyl alcohol gives rise to products involving a rearrangement of the carbon structure.

The most striking feature of this comparison is the large decrease in reactivity associated with the *neo*pentyl halide. The rate relationships for the first four members are fairly normal for the bimolecular mechanism, for which the rate is decreased by electron-accession to the reaction centre, but the *neo*pentyl structure has obviously introduced an effect which is far larger than that to be expected on the basis of the capacity for electron-release of its methyl groups.

In seeking an explanation for this influence we have considered the theory which postulates an electromeric polarisation due to β-hydrogen atoms, $H{-}\overset{\curvearrowright}{C}{-}\overset{\curvearrowright}{C}{-}Br$: this would facilitate the separation of the halogen, and decrease in importance as the β-hydrogen atoms are replaced. Such an effect has been shown to be very important in certain cases (Baker and Nathan, J., 1935, 1844; Hughes, Ingold, Masterman, and MacNulty, J., 1940, 899; Hughes, Ingold, and Taher, *ibid.*, p. 949; Baker, *Trans. Faraday Soc.*, 1941, **37**, 632; Hughes and Ingold, *ibid.*, p. 657; Baker and Hemming, J., 1942, 191); and, since there are no β-hydrogen atoms available in the *neo*pentyl structure, an explanation on this basis is, superficially, of the right form. A detailed consideration shows, however, that it is inadequate in the present instance. First, the electromeric factor

* Reactions of alkyl halides with silver salts in hydroxylic solvents follow modified forms of the general mechanisms (cf. this vol., p. 169).

† This conclusion, and the results on which it was based, were reported in a preliminary form for the Faraday Society's discussion on "Mechanism and Chemical Kinetics of Organic Reactions in Liquid Systems" in September 1941 (cf. *Trans. Faraday Soc.*, 1941, **37**, 603). In a paper submitted to the American Chemical Society at about the same time, and published soon afterwards (*J. Amer. Chem. Soc.*, 1942, **64**, 543), Bartlett and Rosen concluded that the "*neo*pentyl effect" referred to reactions of the S_N2 type and was of a steric nature. Evans and Polanyi (*Nature*, 1942, **149**, 608, 665) adopted a similar explanation, and concluded that the steric factor is largely responsible for the comparative inactivity, in bimolecular replacement reactions, of the *tert.*-butyl halides.

TABLE I.

Absolute and Relative Rates for the Bimolecular Substitution Reactions of Primary Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.

[Bromide] ~0·05M, [NaOEt] ~0·08M; k_2 = second-order constant in sec.$^{-1}$ g.-mol.$^{-1}$ l.

Bromide	Methyl.	Ethyl.	*n*-Propyl.	*iso*Butyl.	*neo*Pentyl.
$10^5k_2^{55°}$	34·4 [1]	1·95 [2]	0·547 [2]	0·058 [2]	8·26 × 10^{-6} [4]
Relative rates at 55°	17·6	1	0·28	0·030	4·2 × 10^{-6}
$10^5k_2^{95°}$	965 [1]	64·7 [5]	—	2·62	6·49 × 10^{-4}
Relative rates at 95°	15	1	—	0·041	1·0 × 10^{-5}

[1] Calculated from experiments at lower temperatures.
[2] Hughes, Ingold, Masterman, and MacNulty, J., 1940, 899.
[3] Experiments by M. L. Dhar and S. Masterman. Their work, which was mainly a study of elimination reactions, will be published in detail later (cf. Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657).
[4] Calculated from experiments at higher temperatures.
[5] Calculated from the results at 55°, assuming an activation energy of 21 kg.-cals. Grant and Hinshelwood (J., 1933, 258) obtained this value for the activation energy of the reaction of ethyl bromide with potassium hydroxide in ethyl alcohol. There is strong evidence that the reaction with alcoholic potash is substantially the same as that with alcoholic sodium ethoxide. Thus, the former reagent, acting on alkyl halides, gives mainly ethers (reaction with $\bar{O}Et$) and not alcohols (reaction with $\bar{O}H$) (Hughes, Ingold, Masterman, and MacNulty, *loc. cit.*).

should produce a steadier logarithmic decrease in rate from ethyl to *neo*pentyl, and could not interpret the much enlarged gap in the rate sequence between *iso*butyl and *neo*pentyl. Secondly, the loss of β-hydrogen is just as complete in methyl as in *neo*pentyl; yet the methyl halides are highly reactive in bimolecular substitutions, whilst the ethyl halides, in spite of the presence of three β-hydrogen atoms, have a considerably reduced rate of reaction in such substitutions; the effect is even more pronounced in *iso*propyl and *tert.*-butyl halides, although the number of β-hydrogen atoms is still greater (many previous papers of this series). Thirdly, since structural influences which facilitate the separation of halogen as an anion always have a much more pronounced effect on the rates of reactions proceeding by the unimolecular mechanism than on rates by the bimolecular mechanism, the electromeric effect of the β-hydrogen atoms should operate more strongly in the former mechanism than in the latter. But we show in Part XXXI (this vol., p. 171) that the reactivity of *neo*pentyl bromide towards an ionisation mechanism is normal. Finally, Bartlett and Rosen have shown (see footnote, p. 158) that this marked effect of the *tert.*-butyl group attached to the α-carbon atom in *neo*pentyl bromide is not primarily due to the operation of any influence of a polar character, since the effect (which they observed in the bimolecular halogen-exchange reaction, RBr + KI ⟶ RI + KBr) is not capable of transmission through an unsaturated linkage (—C≡C—) interposed between the *tert.*-butyl group and the reaction centre. It is therefore concluded that, in addition to the inductive effect of methyl substituents, there is a superposed effect of a non-polar character, which may in principle enter in all stages of methyl substitution, but which amongst the structures studied, assumed outstanding importance only in the case of the *neo*pentyl structure. This effect is concluded to be of steric origin. It is illustrated further in the next paper by reference to the halogen exchange reaction. A theoretical discussion of the effect is contained in Part XXXII (this vol., p. 173).

Arrhenius Parameters.—It is of interest to analyse some of the large differences of rate observed in the present work in terms of the parameters of the Arrhenius equation, $k = Ae^{-E/RT}$. The results of this analysis are given in Table II, where A is in sec.$^{-1}$ g.-mol.$^{-1}$ l. and E is in kg.-cals.

TABLE II.

Arrhenius Parameters for the Bimolecular Substitution Reactions of Primary Alkyl Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.

Bromide	Methyl.	Ethyl.*	*iso*Butyl.	*neo*Pentyl.
A	7·2 × 10^{11}	2·1 × 10^{11}	9·5 × 10^{10}	2·3 × 10^{9}
E	20·0	21·0	22·8	26·2

* These values relate to the reaction of ethyl bromide with alcoholic potassium hydroxide (Grant and Hinshelwood, *loc. cit.*) and may be considered to be closely comparable to the other figures in the table [cf. Note 5 to Table I].

We do not claim great accuracy for these values, which are obtained from rate measurements at two temperatures only, but they suffice to show that the rate differences (Table I) are due to changes in both A and E.

EXPERIMENTAL.

Exploratory Experiments on the Formation of Halides from neo*Pentyl Alcohol.*—*neo*Pentyl alcohol was prepared from formaldehyde and *tert.*-butylmagnesium chloride (Samec, *Annalen*, 1907, **351**, 255; Whitmore and Badertscher, *J. Amer. Chem. Soc.*, 1933, **55**, 1559) or by reduction of ethyl trimethylacetate (Richard, *Ann. Chim. Phys.*, 1910, **21**, 323; *Org. Synth.*, **8**, 104), the latter method being, in our opinion, the more satisfactory. It was fractionated through an all-glass (Pyrex) column (length of packed section = 100 cm.; diam. = 2·2 cm.; efficiency equivalent to 15 theoretical plates) of the total-condensation, adjustable take-off type (Whitmore and Lux, *J. Amer. Chem. Soc.*, 1932, **54**, 3448), which was packed with glass helices (cf. Wilson, Parker, and Laughlin, *J. Amer. Chem. Soc.*, 1933, **55**, 2795; Roper, Wright, Ruhoff, and Smith, *ibid.*, 1935, **57**, 954; Young and Jasaitis, *ibid.*, 1936, **58**, 377), and enclosed in a silvered vacuum jacket fitted with an outer, electrically heated air jacket, which was well insulated and designed to give a small temperature gradient between the bottom and the top.* Interaction of the alcohol (b. p. 113°, m. p. 50°) with thionyl chloride,

* Columns of this type were used throughout the work described in this group of papers.

phosphorus pentachloride, hydrogen chloride or hydrogen bromide failed to yield the *neo*pentyl halides (cf. Whitmore and Rothrock, *loc. cit.*), which were therefore prepared from *neo*pentane (see below).

Kinetic Measurements.—*neo*Pentyl bromide, obtained from *neo*pentane *via neo*pentyl chloride (Whitmore and co-workers, *J. Amer. Chem. Soc.*, 1939, **61**, 1585), was fractionated through a 15-plate column; b. p. 105°/760 mm. *iso*Butyl bromide was obtained from a commercial sample by the usual procedure of removing any *tert.*-butyl bromide which may be present (by hydrolysis with water), and subjecting the unhydrolysed material to careful fractionation; the sample used for the measurements had b. p. 90·5—90·7°/740 mm. Methyl bromide was distilled from phosphorus pentoxide immediately before use. Commercial absolute alcohol was dried by the method of Smith (J., 1927, 1288) as modified by Manske (*J. Amer. Chem. Soc.*, 1931, **53**, 1106), and fractionated.

The thermostats were steady to within 0·02°. In all the experiments described in this paper, the method of sealed bulbs was used. A known amount of the halide was dissolved in the solvent containing the desired quantity of sodium ethoxide, and the solution was made up to 100 ml., usually at 0°. Portions of 5 ml. were enclosed in sealed tubes, which were immersed in the thermostat for known times, and broken under 200 ml. of water. The aqueous solution was then acidified with dilute sulphuric acid and its halide-ion content determined electrometrically. As previously noted (Bateman and Hughes, J., 1940, 947), it was observed that the volume of the reaction tube may be of considerable importance, and the comparative measurements were carried out in small bulbs which were designed to minimise the "free" space above the liquid. It was shown that the addition of crushed glass of the same quality as that of the sealed bulbs had no effect on the rate of reaction. The rate coefficients were calculated from the formula

$$k_2 = [1/(a - b)t] \log_e (b/a)[(a - x)/(b - x)]$$

where a and b are the initial concentrations of sodium ethoxide and alkyl halide respectively, and x is the decrease in concentration after time t. The mean values of the rate constants obtained in the comparative experiments are summarised in Table III, and the results of typical experiments are recorded in detail in Table IV. Corrections for thermal expansion between the temperature at which the 5-ml. portions were measured and that of the thermostat have been applied to the mean second-order coefficients of Table III; the results shown in Table IV have not been corrected for expansion.

Since the reaction of *neo*pentyl bromide with alkali in *aqueous* ethyl alcohol is of the first order (rate independent of the alkali concentration; cf. this vol., p. 166), the evidence that the reaction with sodium ethoxide in the water-free medium is of the second order should be emphasised. Evidence to this effect is provided by the constancy of the second-order coefficients obtained in experiments in which the two reactants are present in comparable concentrations (Table IV). With a higher initial concentration of sodium ethoxide, the second-order coefficient is but slightly altered, provided this reactant still remains in reasonably low concentration. When the base is present in large excess the coefficient is considerably reduced (Table III); this effect is, however, quite general for bimolecular reactions of this type (cf. previous papers in this series, *e.g.*, Hughes, Ingold, Masterman, and MacNulty, J., 1940, 903). Confirmation for the bimolecular mechanism was obtained through a study of the reaction products (see below).

TABLE III.

Summary of Second-order Rate Constants for the Substitution Reactions of Alkyl Bromides with Sodium Ethoxide in Dry Ethyl Alcohol.

([Bromide] ~0·05M; k_2 in sec.$^{-1}$ g.-mol.$^{-1}$ l.)

Bromide.	Initial [NaOEt].	Temp.	$k_2 \times 10^5$.	Bromide.	Initial [NaOEt].	Temp.	$k_2 \times 10^5$.
Methyl	0·077N	20·0°	88·2	*neo*Pentyl	0·077N	95·15°	0·0649
,, ...	0·077N	39·95	786	,, ...	0·935N	95·15	0·0476
*iso*Butyl	0·077N	95·15	262	,, ...	0·077N	125·15	0·963

TABLE IV.

Illustrating Determination of Second-order Rate Constants.

(k_2 in sec.$^{-1}$ g.-mol.$^{-1}$ l.)

1. Methyl Bromide at 20·0°. [NaOEt] and [CH_3Br] expressed in ml. of 0·01005N-$AgNO_3$ per 5 c.c. of solution.

t (mins.)	0	45	60	75	90	105	120	135	180
[CH_3Br]	23·35	19·76	18·77	17·81	16·95	16·20	15·47	14·81	12·87
[NaOEt]	37·92	34·33	33·34	32·38	31·52	30·77	30·04	29·38	27·44
$k_2 \times 10^4$	—	8·57	8·52	8·60	8·58	8·50	8·49	8·45	8·62

2. *neo*Pentyl Bromide at 125·15°. [NaOEt] and [Bromide] expressed in ml. of 0·01N-$AgNO_3$ per 5 c.c. of solution.

t (hrs.)	0	24	48	72·5	120	144	168	192·5	218
[Bromide]	23·66	22·42	21·27	20·24	18·44	17·57	16·87	16·02	15·39
[NaOEt]	37·79	36·55	35·40	34·37	32·57	31·70	31·00	30·15	29·52
$k_2 \times 10^6$	—	8·48	8·48	8·35	8·26	8·35	8·21	8·39	8·27
t (hrs.)	240	288	312	354·8	402·8	456	488		
[Bromide]	14·64	13·54	12·88	12·25	11·40	10·31	9·82		
[NaOEt]	28·77	27·67	27·01	26·38	25·53	24·44	23·95		
$k_2 \times 10^6$	8·49	8·41	8·59	8·28	8·25	8·50	8·50		

3. *iso*Butyl Bromide at 95·15°. [NaOEt] and [Bromide] expressed in ml. of 0·01N-$AgNO_3$ per 5 c.c. of solution. The second-order rate constants, k_2, refer to the total reaction (substitution + olefin elimination; cf. below).

t (mins.)	0	2·5	5	7·5	10	13	17	20	30
[Bromide]	25·24	23·74	22·31	20·96	19·88	18·50	16·94	16·11	13·73
[NaOEt]	38·10	36·60	35·17	33·82	32·74	31·36	29·80	28·97	26·59
$k_2 \times 10^5$	—	5·56	5·65	5·79	5·64	5·78	5·84	5·69	5·40
t (mins.)	40	50	60	70	90	120			
[Bromide]	11·40	9·69	8·49	7·51	5·93	4·19			
[NaOEt]	24·26	22·55	21·35	20·37	18·79	17·05			
$k_2 \times 10^5$	5·53	5·63	5·52	5·45	5·35	5·37			

Olefin Estimations.—In the case of *iso*butyl bromide, a bimolecular elimination reaction, leading to formation of olefin, accompanies the bimolecular substitution reaction, and it was necessary to determine the extent of the elimination process in order to decompose the total second-order rate coefficients into their separate components. At certain stages of reaction, or after its conclusion, a number of bulbs were simultaneously removed from the thermostat; some of these were used in the estimation of the extent of the total reaction as indicated in the preceding section, and the remainder for olefin analysis by the extraction method described by Hughes, Ingold, Masterman, and MacNulty (J., 1940, 899). At 95·15°, the mean of several determinations indicated that olefin elimination accounted for 58·2% of the total reaction; the remaining 41·8% is due to the substitution reaction, and this figure was used to calculate the rate constant recorded in Table III.

Reaction Products from neo*Pentyl Bromide.*—*neo*Pentyl bromide (0·7 g.), and sodium ethoxide (0·935N) in dry ethyl alcohol (5 ml.) were heated in a sealed tube at 125° for 760 hours. The tube was then cooled and opened, its contents were diluted with water (15 ml.), and the mixture was distilled from a small Claisen flask. The first twelve drops of the distillate were mixed with a concentrated solution of calcium chloride (2 ml.) and the upper layer (*ca.* 0·5 ml.) was removed with the aid of a micro-pipette. The second twelve drops, treated similarly, yielded only about 0·1 ml. of a top layer, and a third fraction remained homogeneous. The combined upper layers were distilled from fused barium oxide and twice from potassium; m. p. (Emich's method) 91·5°/760 mm., $n_D^{20°}$ 1·3805 (Found: C, 72·5; H, 13·8. Calc. for $C_5H_{11}OEt$: C, 72·4; H, 13·8%). [Ethyl *neo*pentyl ether has b. p. 90·5°/740 mm. and $n_D^{20°}$ 1·3808 (Whitmore, Wittle, and Popkin, *J. Amer. Chem. Soc.*, 1939, **61**, 1586), and ethyl *tert.*-amyl ether has b. p. 101°/760 mm. and $n_D^{20°}$ 1·3912 (Evans and Edlund, *Ind. Eng. Chem.*, 1936, **28**, 1186.]

The product obtained from the above experiment is evidently ethyl *neo*pentyl ether; no other compound could be isolated. In experiments especially designed to detect *neo*pentane or other volatile compounds (cf. p. 158), it was shown that the maximum yield of gaseous product was under 3%.

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[*Received, August 28th*, 1945.]

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45. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXVII. The Rôle of Steric Hindrance. (Section B) A Comparison of the Rates of Reaction of Ethyl and* neo*Pentyl Bromides with Inorganic Iodides in Acetone Solution.*

By I. DOSTROVSKY and E. D. HUGHES.

A comparison of the rates of reaction of ethyl and *neo*pentyl bromides with inorganic iodides in acetone solution has been made. This reaction is again of the bimolecular type, and, when the results are compared with those obtained for the reaction with sodium ethoxide in alcohol (preceding paper), it is found that the *neo*pentyl structure is responsible for a similarly large decrease of rate in both cases. An analysis of the complications which may arise in the halogen-exchange reaction is given. The main results are discussed in Part XXXII.

IN the preceding paper it was shown that *neo*pentyl bromide is, by comparison with other primary alkyl bromides, extremely unreactive in its bimolecular reaction with sodium ethoxide in ethyl alcohol [some relative rates at 55° were as follows: $(CH_3)_3C{\cdot}CH_2Br$, 1; $CH_3{\cdot}CH_2{\cdot}CH_2Br$, $6·6 \times 10^4$; $CH_3{\cdot}CH_2Br$, $2·4 \times 10^5$]. In order to ascertain if such behaviour is characteristic of bimolecular substitution generally, it is necessary to consider comparative data of a similar type relating to other reactions proceeding by this mechanism. After the completion of our work on the reaction with sodium ethoxide, Bartlett and Rosen published the results of an investigation of the rates of reaction of *neo*pentyl bromide, and of certain other alkyl bromides, with potassium iodide in acetone solution (*J. Amer. Chem. Soc.*, 1942, **64**, 543; cf. this vol., p. 157). This reaction is also of the bimolecular type, and is clearly suitable for comparison with the ethoxylation process.

Qualitatively, the work of Bartlett and Rosen shows that *neo*pentyl bromide exhibits a similarly inert behaviour towards potassium iodide; but the magnitude of the "*neo*pentyl effect" appears, from their results, to be much smaller than in the reaction with sodium ethoxide. These authors compared the reactions of *neo*pentyl bromide and *n*-butyl bromide at 25°. Since our alkyl series did not include *n*-butyl bromide, a rigorous comparison of their data and ours cannot be made; but, as the results of other investigations indicate that the rate differences between *n*-propyl bromide and *n*-butyl bromide are invariably small in bimolecular substitutions (Hughes and Ingold, J., 1935, 244; Hammett, "Physical Organic Chemistry," McGraw Hill Book Co., Inc., N.Y., 1940, p. 154; McKay, *J. Amer. Chem. Soc.*, 1943, **65**, 702), we may obtain a good indication of the position by comparing our ratio (1/66,000) for the ethoxide reactions of *neo*pentyl and *n*-propyl bromides with Bartlett and Rosen's ratio (1/470) for the iodide reactions of *neo*pentyl and *n*-butyl bromides. It would thus appear that the "*neo*pentyl effect" for the reaction with potassium iodide at 25° is smaller than that for the reaction with sodium ethoxide at 55° by a factor of the order of 10^2. Since the reactions involving *neo*pentyl bromide have higher activation energies than those of the other halides under discussion (see below, and the preceding paper), the difference would be even greater if the comparisons referred to the same temperature. An identical factor for the *neo*pentyl effect in two different reactions is not to be expected, even when these reactions proceed by the same mechanism, but we did not anticipate quite such a large difference between the two processes under consideration, and therefore decided to examine the reactions of ethyl bromide and *neo*pentyl bromide with metallic iodides in acetone solution. The results are recorded in this paper.

The reactions of alkyl chlorides and bromides with metallic iodides are, in principle, always reversible, $RBr(Cl) + MI \rightleftharpoons RI + MBr(Cl)$, but in acetone solution the solubilities of the chlorides and bromides of

some of the metals usually employed are small (the iodides are generally much more soluble), and the formation of the organic iodide is thereby greatly favoured. The solubility factor is important when, for example, the iodides of sodium and potassium are used, but it is unimportant in the case of lithium, because the halides of lithium are comparatively soluble and the solution with this cation remains homogeneous throughout reaction.

With *neo*pentyl bromide and sodium iodide, fairly good second-order coefficients for the first 60% of reaction were obtained by using the ordinary second-order rate equation

$$k_2 = [1/(a - b)t] \log_e [b(a - x)/a(b - x)]$$

where a and b are the initial concentrations of the reactants, and x is the decrease in the concentration of either after time t. Similar results were obtained with potassium iodide. When allowance is made for small differences in the initial concentrations of the inorganic iodides (see experimental section), the rate coefficient found in both cases was approximately the same as that obtained from a study of the first third of the homogeneous, and therefore much more reversible, reaction with lithium iodide. As is usual for these reactions, the second-order coefficient decreases somewhat when the initial concentration of the inorganic iodide is increased (cf. Hughes, Juliusburger, Masterman, Topley, and Weiss, J., 1935, 1525; and the experimental section of this paper).

At a temperature for which a direct comparison with *neo*pentyl bromide could be made (64°), the reaction of ethyl bromide with sodium iodide was rapid and reversible, equilibrium being reached in about 20 minutes with the formation of approximately 85% of the theoretical yield of ethyl iodide. The results obtained were slightly erratic in that the second order rate coefficients calculated from the analysis of various reaction tubes occasionally showed considerable divergence, especially after about the first third of the reaction had been completed (see below). In order to minimise both this disturbance and the effect of reversibility, detailed measurements, from which the rate coefficients adopted in our discussion were deduced, were confined to the first 30% of reaction. Similar results were obtained with potassium iodide, but the mean value of the rate coefficient was somewhat lower (see Table I, below) than for the reaction with sodium iodide. The reaction of ethyl bromide with lithium iodide at 64° came to rapid equilibrium with the formation of about 10% of ethyl iodide, and it could not be accurately followed; but it was shown that the rate coefficient calculated from measurements of initial rates at two lower temperatures (0° and 20°) was comparable with the coefficients deduced for the reactions with sodium and potassium iodides (Table I).

The variation of rate in the measurements with sodium and potassium iodides is probably to be ascribed mainly to the heterogeneous nature of the reactions. The rate of formation of the organic iodide would be expected to be free from complications due to reversibility if the inorganic bromide was precipitated more or less completely and instantaneously. The salt formed has, however, an appreciable solubility, and, furthermore, the solution may at times become supersaturated, resulting in a non-reproducible apparent decrease of rate. The same difficulty does not arise to the same degree in the case of *neo*pentyl bromide, partly because the relative rates of the opposing processes are more favourable to the forward reaction, and partly because the reaction is slow enough greatly to reduce complication due to supersaturation.*

Another factor which arises from the heterogeneous nature of the reaction with sodium and potassium iodides has been detected, namely, that the separation of the inorganic bromides involves co-precipitation of inorganic iodide. Since we use the miniature sealed tube technique for the heterogeneous processes (cf. experimental section), this factor cannot vitiate our analytical procedure for estimating the total iodide ion concentration in aliquot portions of the reaction mixture (which was initially homogeneous); but it has some influence on the effective concentration of the inorganic iodide in solution, and therefore on the second-order rate coefficients calculated on the assumption that the whole of the iodide remains dissolved. In general, the disturbance is not serious, as is shown by the result that the rate coefficients for the reactions with sodium and potassium iodides are usually about the same as those obtained for the homogeneous reaction with lithium iodide (cf. Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 476; and also our results for *neo*pentyl bromide). The effect on the rate coefficients will, however, depend to some extent on the supersaturation factor, and on the nature of the precipitated salt and its state of aggregation during the period of reaction, so that somewhat variable results may be obtained in certain cases as already described.

The main results of the investigation are summarised in Table I, where the rate coefficients are in sec.$^{-1}$ g.-mol.$^{-1}$ l.

If we neglect small differences in the concentrations of the reagents employed in some of the experiments (cf. experimental section), the ratios for the rates of reaction of the bromides with the inorganic iodides specified are as shown in the last row of the table. Notwithstanding the complications referred to, and the lack of complete agreement between the results for the various iodides, the approximate value of the "*neo*pentyl effect" in this reaction cannot be in doubt. If we adopt the figure 2×10^4 as the average value for the ratio of the rates at 64°, we may conclude that it is smaller than the corresponding ratio for the rates of reaction of the same two bromides with sodium ethoxide at 55° by a factor of 12. For equal temperatures the factor would be smaller (cf. p. 161).

* A disturbance of this type will undoubtedly be dependent both on the rate of precipitation and on the rate of reaction; it will be of serious consequence if a considerable part of the reaction is completed before the formation of nuclei has occurred, and the conditions governing rapid precipitation have been reached.

TABLE I.

Comparison of the Rates of Reaction of Ethyl and neo*Pentyl Bromides* (RBr) *with Metallic Iodides* (MI) *in Acetone Solution at* 64°.

([RBr] and [MI] ~0·05M.)

Reaction.	(1) RBr + NaI.	(2) RBr + KI.	(3) RBr + LiI.
10^3k_{EtBr}	69	48	45 *
$10^3k_{C_5H_{11}Br}$	0·0031	0·0027	0·0028
$k_{EtBr}/k_{C_5H_{11}Br}$	$2·2 \times 10^4$	$1·8 \times 10^4$	$1·6 \times 10^4$

* Calculated from experiments at lower temperatures.

The Arrhenius activation energy of the reaction of *neo*pentyl bromide with sodium iodide is found to be approximately 25 kg.-cals., whereas that for ethyl bromide and lithium iodide is 19 kg.-cals. These figures are deduced from measurements at two temperatures only, and may be subject to considerable error; nevertheless, it may be safely concluded that the comparative inactivity of *neo*pentyl bromide in bimolecular halogen exchange is largely due to an increase in the activation energy of the reaction. A discussion of these facts is given in Part XXXII (this vol., p. 173). Further work on the halogen-exchange reactions of alkyl halides is in progress.

EXPERIMENTAL.

Materials.—Acetone was purified by the method of Conant and Kirner (*J. Amer. Chem. Soc.*, 1924, **46**, 245), and fractionated through a seven-plate column. The inorganic halides were dried in a vacuum at 140° in an Abderhalden apparatus. *neo*Pentyl bromide was obtained as described in the preceding paper. Ethyl bromide was obtained from a commercial sample, which was purified by fractionation through a 15-plate column; b. p. 37·9—38·1°/760 mm.

Kinetic Methods.—For the experiments with ethyl bromide and lithium iodide, a weighed quantity of the inorganic halide was dissolved in acetone in a graduated flask at 0° or 20°, about 0·5 ml. of the organic halide was added, and the solution was made up to 100 ml. with solvent which had attained the thermostat temperature. At suitable intervals aliquot portions of the reaction mixture were withdrawn and estimated by a modification (see below) of Lang's "iodine cyanide" method (*Z. anorg. Chem.*, 1922, **122**, 332; 1925, **142**, 229, 279; **144**, 75). In the experiments with sodium and potassium iodides, solutions of the organic and inorganic halides were made up separately at room temperature. Portions of 5 ml. of the ethyl bromide solutions were then introduced into small tubes which were cooled to *ca.* — 80°. Then 5 ml. of the solution of the inorganic iodide were added to each, and the tubes sealed and kept at *ca.* — 80° until required. For the rate measurements, the small sealed tubes were immersed in the thermostat for known times, and the contents estimated as in the experiments with lithium iodide. The initial concentration of ethyl bromide was determined in all cases by quantitative hydrolysis of aliquot portions of the reaction mixtures with alkali in small sealed tubes at 95°. For *neo*pentyl bromide, weighed quantities of the organic and the inorganic halides were used to make up

TABLE II.

Summary of Second-order Rate Coefficients for the Reaction of Ethyl and neo*Pentyl Bromides* (RBr) *with Metallic Iodides* (MI) *in Acetone Solution.*

(k_2 in sec.$^{-1}$ g.-mol.$^{-1}$ l.)

Reactants.		RBr.	MI.	Temp.	10^3k_2.	Reactants.		RBr.	MI.	Temp.	10^3k_2.
$C_5H_{11}Br$	NaI	0·07M	0·10M	95·2°	0·062	EtBr	NaI	0·04M	0·03M	64·05°	69
,,	,,	0·07M	0·05M	95·2	0·075	,,	KI	0·04M	0·03M	64·05	48
,,	,,	0·07M	0·05M	64·05	0·0031	,,	LiI	0·05M	0·07M	20·0	0·65
,,	KI	0·05M	0·07M	64·05	0·0027	,,	,,	0·05M	0·07M	0·0	0·061
,,	LiI	0·05M	0·07M	64·05	0·0028						

TABLE III.

Illustrating Determination of Second-order Rate Coefficients.

(k_2 in sec^{-1}. g.-mol.$^{-1}$ l.)

1. Reaction of *neo*Pentyl Bromide with Sodium Iodide. [RBr] and [NaI] expressed in ml. of 0·01665N-KIO_3 per 5·41 ml. sample.

(*a*) Temperature = 95·2°.

t (hrs.)	0	17·5	20·5	25·0	41·0	42·0	43·0	43·83	89·0	89·15
[RBr]	23·34	20·32	19·71	19·01	16·73	16·79	16·65	16·53	13·04	13·00
[NaI]	17·04	13·02	12·41	11·71	9·43	9·49	9·35	9·23	5·74	5·70
10^3k_2	—	6·27	6·41	6·32	6·54	6·30	6·34	6·39	6·44	6·49

(*b*) Temperature = 64·05°.

t (hrs.)	0	171	268	451	668	1492	1860
[RBr]	23·03	21·04	20·19	18·69	17·28	14·26	13·14
[NaI]	15·57	13·58	12·73	11·23	9·82	6·80	5·68
10^4k_2	—	3·00	2·96	3·06	3·08	2·80	2·89

2. Reaction of Ethyl Bromide with Sodium Iodide at 64·05°. [RBr] and [NaI] expressed in ml. of 0·01665N-KIO_3 per 10·00 ml. sample.

t (mins.)	0	0·5	0·75	1·00	1·00	1·5	11·5	2·0
[RBr]	24·10	22·56	22·10	21·48	21·52	20·46	20·56	19·51
[NaI]	18·34	16·80	16·34	15·72	15·76	14·70	14·80	13·75
10^3k_2	—	7·60	6·66	6·76	6·56	6·66	6·45	6·66

a standard mixture at 0°; 5 ml. portions were then sealed in small bulbs, and the reaction followed as described for ethyl bromide. Lang's method of estimation had to be slightly modified for our purpose in order to avoid interference due to the presence of acetone.* Our procedure was as follows: The sample was diluted with 100 ml. of ice-cold water, the aqueous solution was then acidified with 20 ml. of a cold aqueous mixture of sulphuric and hydrochloric acids (12N in H_2SO_4 and 3N in HCl), 5 ml. of 15% aqueous potassium cyanide were added, and the mixture titrated with standard potassium iodate solution, using starch as indicator. Initial or "zero" readings were obtained by the analysis of samples which had been kept in the thermostat for periods sufficient for them to attain the correct temperature.

The most important features of the results are illustrated in the tables on p. 163. The mean second-order coefficients recorded in Table II are corrected for thermal expansion between the temperature at which the samples were measured and that of the thermostat. The results for a few typical experiments shown in Table III have not been corrected for expansion, but this does not, of course, alter the relative values of the coefficients of any one experiment.

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46. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXVIII. The Rôle of Steric Hindrance. (Section C) A Comparison of the Rates of Reaction of Methyl, Ethyl,* n-*Propyl,* iso*Butyl, and* neo*Pentyl Bromides with Aqueous Ethyl Alcohol.*

By I. DOSTROVSKY and E. D. HUGHES.

A comparison has been made of the rates of solvolysis of the halides, named in the title, in "50%" aqueous ethyl alcohol at 95°. The rate sequence is again found to be Me > Et > *n*-Pr > *iso*Bu ≫ *neo*pentyl, but the rate differences (relative rates: Me 2·0, Et 1, *n*-Pr 0·57, *iso*Bu 0·080, *neo*pentyl 0·0065) are smaller than those observed for the bimolecular reaction with sodium ethoxide, the difference between *iso*butyl and *neo*pentyl being very much smaller (cf. p. 157). It is shown that the solvolytic reactions of the first four halides are largely bimolecular, but the results for *neo*pentyl bromide support an ionisation mechanism (cf. following paper). On the basis of the duality of mechanism, the rate data for the solvolytic process can be explained, both in relation to the alkyl series, and by comparison with the results for the bimolecular reaction with sodium ethoxide. Some special aspects of the results are discussed further in Part XXXII (p. 173).

HAVING obtained a comparison of the reactivity of *neo*pentyl and other primary bromides in their bimolecular reactions with sodium ethoxide in absolute ethyl alcohol (this vol., p. 157) and with sodium iodide in acetone (this vol., p. 161), it was of interest to institute a similar comparison with respect to other conditions of reaction; particularly those more favourable to a preliminary ionisation of the alkyl halides. Relatively to the bimolecular process, an ionisation mechanism should be facilitated by an increase in the ionising capacity of the solvent and by a decrease in the nucleophilic activity of the reagent (Hughes and Ingold, J., 1935, 244, and later papers). We therefore examined the solvolytic reactions of the bromides named in the title, in "50%" aqueous alcohol † in the absence of alkali or any other reagent of high nucleophilic activity. The results are now described.

The first-order rate coefficients (in sec.$^{-1}$) at 94·85° are listed in Table I; the second-order rate coefficients (in sec.$^{-1}$ g.-mol.$^{-1}$ l.) at 95° for the reactions with sodium ethoxide in absolute alcohol (*loc. cit.*) are included for comparison.

TABLE I.

(1) = Bimolecular reaction with NaOEt in EtOH. (2) = Solvolytic reaction in "50%" H_2O–EtOH.

Alkyl bromide.	10^4k for (1).	10^4k for (2).	Alkyl bromide.	10^4k for (1).	10^4k for (2).
Me	9650	2·86	*iso*Bu	26·2	0·113
Et	647	1·41	*neo*Pentyl	0·00649	0·00910
n-Pr	181 *	0·803			

* Estimated from results at 55° (this vol., p. 157), the ratio $k_{EtBr}/k_{n\text{-}PrBr}$ being assumed to be independent of temperature.

If we imagine the sodium ethoxide concentration to be buffered to N, the figures of the first and the second row become directly comparable, the former now becoming first-order constants under the mass law. The kinetic order of the solvolytic reaction gives by itself no information concerning mechanism. If, however, the solvolytic reaction followed a bimolecular course throughout the series of halides, the change of conditions from (1) to (2) should cause a large decrease of rate in all cases, because of the decrease in the nucleophilic activity of the substituting agent. For the first four members of the series the observed rates do decrease from (1) to (2). We also have independent evidence that the solvolytic reactions of these four compounds are largely bimolecular. Of the four, *iso*butyl should be most prone to react by the unimolecular mechanism; yet we have shown that added alkali produces a large increase in the rate of its hydrolysis in 50% aqueous ethyl alcohol (experimental section). An analysis of the results by the method previously used to demonstrate that the solvolytic reactions of methyl bromide and ethyl bromide in aqueous ethyl alcohol are bimol-

* Senior, Hetrick, and Miller (*J. Amer. Chem. Soc.*, 1944, **66**, 1987) have recently referred to the inaccuracy of Andrews's similar method in the presence of acetone.

† See Experimental section.

ecular (Bateman, Cooper, Hughes, and Ingold, J., 1940, 925) shows that the reaction of *iso*butyl bromide is predominantly of the same type.* For *neo*pentyl bromide the rate constant for reaction (2) is slightly greater than that for reaction (1). This could be explained if the bimolecular mechanism, operative for reaction (1), has here been replaced by a unimolecular mechanism in the case of reaction (2). Evidence in support of an ionisation mechanism for the solvolysis of *neo*pentyl bromide in aqueous ethyl alcohol is contained in the following paper.

On the basis of the duality of mechanism, the results for the solvolytic reaction can be explained, both in relation to the alkyl series, and by comparison with the results for the bimolecular reaction with sodium ethoxide. The rate variation among the members of the series is similar in type in both cases, except that the rate differences for the solvolytic process are smaller than those for the reaction with sodium ethoxide, and that the difference between *iso*butyl bromide and *neo*pentyl bromide is very much smaller; so much so that the latter compound, although still the slowest of the halides, is much less peculiar with respect to its behaviour in solvolysis than in the reaction with ethoxide ions. The rate relationships for the solvolytic reactions of the first four halides are consistent with the evidence that these reactions are predominantly, though probably not wholly, bimolecular (cf. Part XXVI). However, for the last member of the series, the rate, instead of dropping to an immeasurably small value, as it would were the reaction bimolecular, drops only to about one-twelfth of that for *iso*butyl bromide, this value representing, according to our explanation, the unimolecular rate (rate of ionisation) of *neo*pentyl bromide. It should be emphasised that this unimolecular rate is observed in a highly aqueous solvent, and that it would be much smaller in dry ethyl alcohol, the solvent used for the study of the alkaline reaction. Some further aspects of these results, particularly the absence of any large steric effect in the unimolecular reaction of the *neo*pentyl halide, are discussed in accompanying papers (see, especially, this vol., p. 173).

Experimental.

Materials.—*n*-Propyl bromide was obtained by fractionation of a commercial sample through a 15-plate column; the fraction used for the measurements had b. p. 70·9—71·1°/760 mm. In the case of the other halides, samples obtained as described in the preceding papers were used. The solvent labelled "50%" aqueous ethyl alcohol was obtained by mixing, at room temperature, equal volumes of dry ethyl alcohol (this vol., p. 160) and distilled water.

Rate Measurements.—The technique employed was similar to that described in Part XXVI (this vol., p. 157), but, with two exceptions, the halides were always examined in initially neutral solution. One exception was *neo*pentyl bromide, for which it was generally convenient to dissolve in the medium sufficient sodium hydroxide to maintain the solution alkaline throughout the runs. The presence of the base has no influence on the rate of solvolysis of this halide, and it prevents the incursion of a reaction between the medium and hydrogen bromide, which in this case becomes troublesome in initially neutral solutions (following paper). The other exception was *iso*butyl bromide, for which it was necessary to determine the magnitude of the effect of added alkali through a comparison of the rates in basic, and in neutral or acidic, solutions (cf. below, and the theoretical section of this paper). The initial concentrations of the alkyl halides were approximately 0·05N throughout.

Rates of Solvolysis of Alkyl Halides in "50%" Aqueous Ethyl Alcohol at 94·85°.—In the following record of detailed experiments (Table II), which are typical of the series of solvolytic reactions studied, the concentrations of the alkyl halides are expressed in equivalent ml. of 0·010N-silver nitrate per 5 ml. of solution, and the first-order rate coefficients are in sec.$^{-1}$.

Table II.

(a) iso*Butyl bromide.*

t (hrs.) ...	0	1·0	2·0	3·25	4·0	4·25	5·25	7·0	14·6	17·0	19·75	23·5
[RBr] ...	24·41	23·36	22·48	21·23	20·70	20·45	19·73	18·50	13·33	12·63	10·99	10·32
$k_1 \times 10^5$	—	1·22	1·15	1·19	1·15	1·16	1·13	1·10	1·15	1·08	1·12	1·02

(b) *Ethyl bromide.*

t (mins.)	0	5	11	14	16·5	19	25	33	46	61	75	95
[RBr] ...	22·75	21·79	20·72	20·30	19·91	19·38	18·34	17·08	15·70	13·20	12·26	9·96
$k_1 \times 10^4$	—	1·44	1·42	1·36	1·35	1·41	1·44	1·45	1·37	1·49	1·38	1·45

Rate of Hydrolysis of iso*Butyl Bromide with Alkali in "50%" Aqueous Ethyl Alcohol at* 94·85°.—In order to show that the rate of hydrolysis of *iso*butyl bromide is influenced by alkali, a kinetic run was carried out in the presence of 0·11M-sodium hydroxide. The mean second-order rate coefficient of the total reaction was found to be $2·73 \times 10^{-3}$ sec.$^{-1}$.g.-mol.$^{-1}$ l. Under these conditions an elimination reaction leading to olefin formation accompanies the substitution process; and olefin determinations, carried out on the products of a completed hydrolysis, as described in Part XXVI (this vol., p. 161), indicated that the elimination process accounts for 37·5% of the total reaction. The second-order rate coefficient for the substitution reaction is thus $(62·5/100) \times 2·73 \times 10^{-3} = 1·71 \times 10^{-3}$ sec.$^{-1}$ g.-mol.$^{-1}$ l. Comparing this result with the determined first-order rate coefficient of the solvolytic reaction ($k_1 = 1·13 \times 10^{-5}$ sec.$^{-1}$), it is obvious that the rate of hydrolysis of *iso*butyl bromide is greatly increased by alkali.

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[*Received, August 28th,* 1945.]

* Taking account of the concentration of the solvent for the purpose of an order-of-magnitude calculation, it was shown (Bateman, *et al., loc. cit.*) that the specific rate which would have to represent the activity of water and alcohol in an assumed bimolecular reaction with the methyl and ethyl halides is about 10^{-5} times smaller than the corresponding rate for the reaction with hydroxide and ethoxide ions; and this is consistent with the known relationships between specific rate and basic strengths established by Brönsted and others. The rate disparity for *iso*butyl bromide is smaller (factor *ca.* 10^{-4}), and this may indicate a slight tendency towards unimolecular solvolysis in the case of this halide. However, we may conclude that the reactions of the first four members of the halide series under discussion are largely bimolecular.

47. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXIX. The Rôle of Steric Hindrance. (Section D) The Mechanism of the Reaction of* neo*Pentyl Bromide with Aqueous Ethyl Alcohol.*

By I. Dostrovsky and E. D. Hughes.

The work described in the foregoing papers gave an indication that the reaction of *neo*pentyl bromide in aqueous ethyl alcohol involved a preliminary, rate-determining ionisation of the halide (cf. especially, the preceding paper). Since the ionisation mechanism had not previously been observed with certainty in primary halide structures, and the rate of ionisation of *neo*pentyl bromide was of particular interest in connection with the general investigation described in this group of papers (see Abstract on p. 157), we have investigated the mechanism of the solvolytic reaction of this halide in some detail. An ionisation mechanism is confirmed by experiments demonstrating the insensitivity of the rate to the presence of alkali and a characteristic sensitivity to changes in the composition of the mixed solvent—these being diagnostic features shown by the solvolytic reactions of certain other halides (*e.g.*, *tert.*-butyl halides), for which a rate-determining ionisation has been established. Furthermore, the products exhibit rearranged structures—a fact which, when taken in conjunction with the work of Whitmore and others, would also imply the prior formation of a carbonium ion.

In general, the first-order solvolysis of alkyl halides in water–alcohol media may be of the unimolecular type, *e.g.*,

$$\left.\begin{array}{l} R{-}X \xrightarrow{(slow)} \overset{+}{R} + \overset{-}{X} \\ \overset{+}{R} + H_2O \xrightarrow{(fast)} R{-}OH + \overset{+}{H} \end{array}\right\} \quad (S_N1)$$

or of the bimolecular type, *e.g.*,

$$H_2O + R{-}X \longrightarrow R{-}OH + \overset{+}{H} + \overset{-}{X} \quad (S_N2)$$

In previous papers in this series (cf. especially, Bateman, Cooper, Hughes, and Ingold, J., 1940, 925) it has been shown that, although secondary and tertiary halides respectively show a moderate and a well-developed tendency to follow the unimolecular mechanism, yet the common primary halides exhibit such a strong preference for the bimolecular process as to render the unimolecular reaction extremely difficult to isolate.

In Parts XXVI and XXVII (this vol., pp. 157, 161) it was shown that, in *neo*pentyl bromide, reactivity by the bimolecular mechanism is greatly reduced. Since this halide shows considerable reactivity in solvolysis with aqueous alcohol (preceding paper), the hypothesis was entertained that we have here conditions favourable to an ionisation mechanism in a primary halide structure. This hypothesis is now supported by a detailed investigation of the reaction mechanism.

Our evidence of mechanism falls under three heads, (*a*) the effect on reaction rate of the addition of a much stronger nucleophilic reagent than the solvent, (*b*) the effect on reaction rate of increasing the ionising capacity of the solvent, (*c*) the nature of the reaction products. These points will now be discussed.

(*a*) *The Effect of Added Sodium Hydroxide.*—In discussions relating to the various methods available for determining the mechanism of solvolytic reactions for which the reaction order is not itself informative,* we have stressed the importance of the method which depends on the effect on reaction rate of changes in the reagent, and especially on the behaviour of reagents which are much more nucleophilic than the solvent (see, especially, Hughes and Ingold, J., 1935, 244; Bateman, Cooper, Hughes, and Ingold, *loc. cit.*; Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185; 1941, **37**, 603). The simplest and the most conclusive result obtains if these powerful reagents do not influence the rate; it is then inconceivable that the comparatively weakly nucleophilic solvent molecules should function as reagents in the rate-determining process, and the possibility that a bimolecular mechanism may be in operation is thus eliminated for such cases.

In the present application we investigated the effect of various concentrations of sodium hydroxide on the rate of reaction of *neo*pentyl bromide in 70% aqueous ethyl alcohol at 95°; the results are given in Table I.

Table I.

Rates of reaction of neo*pentyl bromide in aqueous ethyl alcohol containing varying concentrations of sodium hydroxide.*

Initially, [RBr] ~0·05N; k_1 is the first-order rate constant (first order with respect to the alkyl halide) in sec.$^{-1}$.

Initial [NaOH], N	0·015	0·075	0·200
$k_1 \times 10^7$	1·54	1·54	1·53

The rate is obviously independent of the concentration of hydroxide ions. These ions, and, *a fortiori*, the solvent molecules, do not function as reagents in the rate-determining stage of the reaction; in short, the results exclude a bimolecular mechanism. The evidence is further strengthened by more detailed reference to

* Since the solvent is in large excess, the reaction will be of the first order irrespective of mechanism, *i.e.*, independently of whether or not the solvent molecules function as reagents in the rate-determining stage of the reaction. Significant departures from first-order kinetics are not to be expected in the case now under investigation (cf. Bateman, Hughes, and Ingold, J., 1940, 960).

the first experiment summarised in the table ([NaOH] = 0·015N). In this instance, the hydroxide ion concentration was not sufficient to maintain the solution alkaline, and it became acidic during the course of the measurements; nevertheless, the calculated first-order rate coefficients were approximately constant throughout the measured range of reaction (cf. experimental section). Good first-order constants were also obtained in the other experiments.

(*b*) *The Effect of Increasing the Water Content of the Medium.*—The effect of solvent variation is, in some respects, not so critical and conclusive as the effect described above, but it provides useful auxiliary evidence of mechanism. Both mechanisms should be facilitated by passing to a more aqueous solvent, but a unimolecular reaction, depending, as it does, on a preliminary rate-determining ionisation of the alkyl halide, should be more strongly influenced by solvation factors than should a bimolecular reaction, wherein solvent molecules participate as effective reagents in the rate-determining process (Bateman, Cooper, Hughes, and Ingold, *loc. cit.*). The difference in the quantitative nature of the effects may be illustrated by reference to available data relating to the methyl, ethyl, *iso*propyl and *tert.*-butyl halides. We give here the approximate ratios of the first-order rate constants in " 60% " and " 80% " aqueous ethyl alcohol ($k_{60\%}/k_{80\%}$) for the solvolytic reactions of the bromides of this series at 25° *: MeBr 2, EtBr 2, Pr$^{\beta}$Br 3, Bu$^{\gamma}$Br 10. There is independent evidence here for the conclusion that a predominantly bimolecular reaction in the case of the first two compounds gives way to a unimolecular reaction in the last, the case of the *iso*propyl halide being of intermediate type (see, especially, Bateman *et al.*, *loc. cit.*). With *neo*pentyl bromide, it will be seen from the figures given in the experimental section that a change from " 70% " to " 50% " aqueous ethyl alcohol produces a six-fold increase of rate at 95°. For a change from 80% alcohol to 60% the factor is likely to be larger, in fact, about 10.† The effect is thus very similar to that for *tert.*-butyl bromide, and this fact may be regarded as evidence in favour of an ionisation mechanism in the case of *neo*pentyl bromide.

(*c*) *The Reaction Products.*—In general, the reaction of an alkyl halide with a reactive solvent gives rise to the same products independently of whether the mechanism is a one-stage bimolecular process or a two-stage unimolecular process involving a preliminary ionisation. Exceptions may, however, arise in the following way: In the bimolecular mechanism, the direct attachment of the reagent, proceeding synchronously with the expulsion of the replaced group, invariably gives rise to a product in which the alkyl group is the same as in the reactant. When an intermediate carbon cation is formed, however, it may in special cases undergo rearrangement, so that the products formed in a subsequent reaction with the solvent may contain an alkyl group structurally distinct from that of the reactant. A study of the reaction products may thus afford a useful criterion of the mechanism of the reaction by which halogen is eliminated from certain alkyl halides, and the *neo*pentyl structure, because of its well-known tendency to undergo rearrangement to give *tert.*-amyl derivatives, is a good case for such a study.

From the bimolecular (S_N2) reaction of *neo*pentyl bromide with sodium ethoxide in dry ethyl alcohol, only ethyl *neo*pentyl ether could be isolated (this vol., p. 157). For the solvolytic reaction with 50% aqueous ethyl alcohol, however, a study of the reaction products under the conditions of our kinetic experiments (at 125°, and in the presence of excess alkali) gave evidence of the formation of ethyl *tert.*-amyl ether and olefin (see experimental section). The yield of olefin thus obtained (36%) is roughly that to be expected on the assumption of the formation of the *tert.*-amyl cation.‡ Under the conditions of our experiments (alkaline medium), it is inconceivable that these products could arise from a bimolecular reaction of the halide with the solvent (to give *neo*pentyl derivatives) followed by subsequent rearrangement. Hence the possibility that the halogen may be eliminated by a bimolecular mechanism is again excluded, and the results are consistent with the assumption of a rate-determining ionisation of the alkyl halide.

The mechanism of this change will be discussed in more detail in Part XXXII, where it will be shown that rearrangement is definitely diagnostic of the setting free of a group with an incomplete carbon octet—in this case, obviously, the *neo*pentyl cation. The rearrangement of this to the *tert.*-amyl cation is subsequent; it will be shown, in another example in which evidence from optical activity is available, that rearrangement follows, rather than accompanies, ionisation, and is therefore a consequence of ionisation, rather than a contributory cause. Thus the measured rate is essentially an ionisation rate, and it is consistent that it is of the order of magnitude we had predicted by extrapolating to primary bromides the ionisation rates of

* Calculated from the results of Hughes, Ingold, *et al.* (J., 1936, 225; 1940, 925) and Taylor (J., 1937, 992). The expression " *x*% " aqueous ethyl alcohol means a mixture made from *x* vols. of anhydrous ethyl alcohol and 100 − *x* vols. of water.

† For *tert.*-butyl chloride, for example, the conversion factor ($k_{60\%}/k_{80\%} \div k_{50\%}/k_{70\%}$) is 1·5 (Hughes, J., 1935, 255).

‡ A comparable figure for the ratio in which the *tert.*-amyl cation, formed as an intermediate in the solvolysis of *tert.*-amyl bromide, is partitioned between olefin elimination and hydrolytic substitution is not available, but it may be roughly deduced in the following way: The unimolecular solvolysis of *tert.*-amyl bromide in " 100% " " 80% " and " 60% " alcohol at 25° gave 36, 26, and 20% olefin (Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657). In " 50% " alcohol at 25° the figure might therefore be about 18%. The effect of increasing the temperature can be assessed from the results of Hughes and MacNulty (J., 1937, 1283) for the influence of temperature variation on the rate constants of elimination and substitution in the unimolecular solvolysis of *tert.*-amyl chloride in " 80% " aqueous ethyl alcohol. Assuming that the partitioning of the *tert.*-amyl cation between elimination and substitution is similarly influenced by temperature when the original reactant is *tert.*-amyl bromide and the solvent " 50% " aqueous ethyl alcohol, it can be shown that the olefin obtainable from the reaction of the bromide with the " 50% " alcohol solvent at 125° should account for about 40% of the total reaction—a figure which is in reasonably good agreement with the value (36%) for the yield of olefin formed from *neo*pentyl bromide under these conditions.

tertiary and secondary bromides; and that in another solvent (Part XXXI) it is of the order of magnitude of the measured rates for other primary bromides, which, in that solvent, we believe to be undergoing unimolecular solvolysis.

Experimental.

Materials.—*neo*Pentyl bromide was prepared and purified as previously described (this vol., p. 157). The "70%" aqueous ethyl alcohol was obtained by mixing, at room temperature, 70 vols. of dry ethyl alcohol (cf. this vol., p. 160) with 30 vols. of distilled water, and "50%" aqueous alcohol was similarly prepared from equal volumes of the constituents. Appropriate quantities of sodium hydroxide were dissolved in the media, and the alkali concentration determined by titration against standard acid.

Kinetic Measurements.—A weighed quantity of the halide, sufficient to yield an approximately 0·05N-solution, was made up to 100 ml. at 0° with alkaline solvent. Portions of 5 ml. were then enclosed in small sealed tubes, which were immersed in the thermostat for known times, and the halide ion content determined as previously described (this vol., p. 160).

The selection of detailed experiments in Table II illustrates the nature of the results from which the rate coefficients are obtained. The first-order constants are calculated by means of the equation, $k_1 = (1/t) \log_e C_0/C_t$, where C_0 and C_t are the concentrations of the alkyl halide at zero time and after t seconds, respectively, and are expressed in ml. of 0·010N-silver nitrate per 5 ml. sample.

Table II.

A. *Medium* "70%" *Aqueous Ethyl Alcohol. Temp.* 95·0°.

(*a*) Initially, [NaOH] = 0·0153N.

t (hrs.)	0	69	144	288	310·5	359	405	503	572	624	672 *
[RBr]	25·57	24·58	25·53	21·82	21·54	21·03	20·50	19·43	18·79	18·13	17·76
$k_1 \times 10^7$	—	1·60	1·60	1·53	1·53	1·52	1·52	1·52	1·50	1·53	1·51

(*b*) Initially, [NaOH] = 0·200N.

t (hrs.)	0	46	118	170	244	337·5	412	556	771
[RBr]	24·23	23·60	22·66	22·02	21·27	20·17	19·37	17·96	15·94
$k_1 \times 10^7$	—	1·58	1·57	1·56	1·49	1·51	1·51	1·49	1·51

B. *Medium* "50%" *Aqueous Ethyl Alcohol. Temp.* 95·15°.

Initially, [NaOH] = 0·075N.

t (hrs.)	0	38·5	86·5	135·5	167·5	215·5	260·75	312·5
[RBr]	23·61	20·74	17·53	14·72	13·32	11·62	9·88	8·47
$k_1 \times 10^7$	—	9·35	9·58	9·58	9·50	9·15	9·30	9·15

C. *Medium* "50%" *Aqueous Ethyl Alcohol. Temp.* 125·15°.

Initially, [NaOH] = 0·075N.

t (hrs.)	0	2	2·8	4·2	5·0	6·0	7·0	8·0	9·0	17·2	18·2
[RBr]	23·28	20·23	19·32	17·77	16·53	15·65	14·49	13·84	12·90	6·95	6·61
$k_1 \times 10^5$	—	1·95	1·85	1·79	1·90	1·84	1·88	1·81	1·83	1·95	1·92

t (hrs.)	19·2	20·2	21·25
[RBr]	6·09	5·95	5·40
$k_1 \times 10^5$	1·94	1·88	1·93

* The solution had become acidic at this point. Owing to the slowness of the hydrolysis, the solvent reacts appreciably with hydrobromic acid during the time required for a completed run, and we were thus prevented from conducting experiments in more strongly acidic media.

Arrhenius Parameters.—From the rate constants in "50%" aqueous ethyl alcohol at 95·15° (mean $k_1 = 9{\cdot}37 \times 10^{-7}$ sec.$^{-1}$) and 125·15° (mean $k_1 = 1{\cdot}88 \times 10^{-5}$ sec.$^{-1}$), the parameters B and E of the Arrhenius equation, $k = Be^{-E/RT}$, are found to be $1{\cdot}5 \times 10^{11}$ (sec.$^{-1}$) and 29·0 (kg.-cals.) respectively.

Reaction Products.—A study of the reaction products was made under the conditions of the kinetic experiments in "50%" aqueous ethyl alcohol at 125°.

Olefin estimations, carried out as described in Part XXVI (this vol., p. 161), showed that olefin formation accounted for 36% of the total reaction.

Owing to the small quantities of products available, a special technique was devised for characterising and estimating the other compounds formed. The method is based on comparisons of colour intensities produced when certain alcohols (not ethyl alcohol) are heated with sulphuric acid and an aromatic aldehyde. The original procedure of Penniman (*Ind. Eng. Chem. Anal.*, 1937, **9**, 91) and Coles (*ibid.*, 1942, **14**, 20) was found, for our purpose, to be too sensitive, and lacking in discrimination between the various products which might be present. The following method was finally adopted: The sample (5 ml.) is diluted to 50 ml. with distilled water, and 5 ml. portions of the dilute solution are placed in boiling-tubes, cooled in ice, and mixed with 25 ml. of 65% sulphuric acid and 2 ml. of a solution containing 1·75 g. of vanillin in 100 ml. of absolute ethyl alcohol. The mixture is then heated on a boiling water-bath for 20 minutes, cooled, and the colour density produced measured by means of a "Hilger Spekker Absorptiometer" against a blank similarly obtained from 5 ml. of alkaline (0·075N) "50%" aqueous ethyl alcohol. In general 6—8 samples were treated simultaneously under the same conditions, one being the blank, while two or more contained solutions of *tert.*-amyl alcohol for comparison. A calibration curve was constructed using a series of standard solutions of *tert.*-amyl alcohol (concentrations = 0·005—0·050M) in the solvent employed in the kinetic studies, but this curve was used only in the preliminary estimation of the products; for increased reliability, the unknown sample was compared with two standard solutions of *tert.*-amyl alcohol, one slightly stronger and one slightly weaker than the test sample.

Preliminary experiments were carried out in order to compare the intensity of the coloration produced when 5-ml. samples of standard solutions (always in the solvent employed in the kinetic runs) of *neo*pentyl alcohol, trimethylethylene, ethyl *tert.*-amyl ether and *tert.*-amyl alcohol were treated as described above. The results are set out below:

Solution tested.	Colour density relative to blank (drum readings).
0·020M-*tert.*-Amyl alcohol	0·35, 0·35, 0·35
0·020M-Ethyl *tert.*-amyl ether	0·30, 0·30, 0·30
0·017M-Olefin	0·05, 0·05, 0·03
0·07M-*neo*Pentyl alcohol	0·03, 0·03, 0·03

Thus, by comparison with *tert.*-amyl alcohol and ethyl *tert.*-amyl ether, which produce very similar results, *neo*pentyl alcohol and trimethylethylene give almost negligible colorations under the conditions used. Further tests, and the use of the calibration curve, showed that a reaction solution (originally containing *neo*pentyl bromide) contained, after completion of the solvolysis, *tert.*-amyl alcohol and *tert.*-amyl ether (taken collectively) in about 0·28M concentration. Five tubes containing the reaction products, together with two standard solutions of *tert.*-amyl alcohol (0·025M and 0·030M) were then similarly treated and tested. By interpolation from the comparisons, assuming linearity in the calibration curve for this narrow region of concentration change, the combined concentrations of *tert.*-amyl alcohol and ether in the samples (neglecting a small correction due to the presence of olefin and treating the alcohol and ether as equivalent in intensity) were thus found to be 0·028, 0·029, 0·030, 0·027 and 0·029M; mean = 0·028$_8$M. The bromide-ion concentration in the reaction tubes was 0·0455M; the results therefore indicate that the *tert.*-amyl substitution products accounted for about 63% of the total reaction.

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48. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXX. The Rôle of Steric Hindrance. (Section E) A Comparison of the Rates of Reaction of Methyl, Ethyl, n-Propyl, isoButyl, and neoPentyl Halides with Silver Nitrate in Aqueous Ethyl Alcohol.*

By I. DOSTROVSKY and E. D. HUGHES.

A comparison has been made of the rates of reaction of the halides, named in the title, with silver nitrate in "70%" aqueous ethyl alcohol. The rate sequence is found to be Me<Et>*n*-Pr>*iso*Bu>*neo*Pentyl, the relative rates (Et = 1) for the bromides at 64° being: Me 0·81, Et 1, *n*-Pr 0·51, *iso*Bu 0·084, and *neo*Pentyl 0·013. By comparison with the results for the bimolecular reaction with sodium ethoxide in dry ethyl alcohol (see Abstract on p. 157), and the solvolytic reaction with 50% aqueous ethyl alcohol (Abstract, p. 164), the sequence of rates for the methyl and ethyl halides is reversed, and the rate differences due to the progressive introduction of β-methyl substituents are, on the whole, smaller than before. The mechanism of the silver reaction is complex, but the available information concerning it is consistent with the conclusion that the effects are associated with an ionisation mechanism, which if fully developed throughout the series should lead to the inequality Me<Et, and might lead to the sequence Me<Et<*n*-Pr<*iso*Bu<*neo*Pentyl (cf. following paper). It seems clear that the ionisation process is a greater influence on the variation of rate in the series as a whole than was the case in the solvolytic reaction. Some special aspects of the results are discussed in Part XXXII (p. 173).

REACTIONS involving the elimination of halogen from organic halides are often carried out with the aid of silver salts in appropriate solvents. The results of investigations concerning the mechanism of these reactions have led to the conclusion that they are mainly heterogeneous, the removal of the halogen by the electrophilic silver ions being facilitated by adsorption of the reagents on the surface of the precipitated silver halide (Hughes, Ingold, *et al.*, J., 1937, 1236, 1243, 1252). The process then depends essentially on an assisted heterogeneous ionisation of the alkyl halide, which is generally succeeded, under the conditions usually employed, by the reaction of the carbon cation with a nucleophilic solvent or solute molecule (*e.g.*, H_2O, NO_3^-). The general resemblance to the homogeneous unimolecular substitution mechanism (S_N1) is then reflected in certain similarities in the characteristic features of the two processes. The analogy of behaviour has been observed particularly in connection with the stereochemical consequences of the substitution processes, and the effects on the reaction rates of structural changes in the organic halide (Hughes, Ingold, *et al., loc. cit.*).

With this impression of the reaction mechanism in mind, we decided to compare the rates of reaction between *neo*pentyl halides and silver nitrate in aqueous ethyl alcohol with the corresponding rates for the halides of the other alkyl groups named in the title. We considered that we could thus assess the comparative reactivities of these compounds towards a reaction which is in common use in organic chemistry, and which may be of such a mechanism as to give an indication of the relative rates under conditions more favourable to ionisation in the alkyl series as a whole than those obtaining in the work described in the preceding papers.

As already implied, the reaction is complex, but it often approximates to one of the second order (Chiminello, *Gazzetta*, 1895, **25**, ii, 410; v. Biron, *J. Russ. Phys. Chem. Soc.*, 1900, **32**, 667; Burke and Donnan, *J.*, 1904, **85**, 555; Senter, *J.*, 1911, **99**, 95). We found this to be the case in our work; for the same initial concentration of the silver salt, the second-order rate coefficients were nearly constant for the greater part of the reaction (cf. experimental section); thus they afford the best means of expressing the comparative reactivities of the halides. The main results of the investigation are summarised in Table I, where k_2 is in sec.$^{-1}$ g.-mol.$^{-1}$ l. The relative rates (Et = 1) for the alkyl bromides are given in Table II, where a comparison is made with the results for two other reactions previously studied (preceding papers).

TABLE I.

*Summary of Second-order Rate Coefficients for the Reaction of Alkyl Halides in "70%" * Aqueous Ethyl Alcohol.*

Halide.	Initial [Halide].	Initial [$AgNO_3$].	Temp.	$k_2 \times 10^4$.	Halide.	Initial [Halide].	Initial [$AgNO_3$].	Temp.	$k_2 \times 10^4$.
MeBr	~0·10M	~0·14M	63·95°	62·5	$CMe_3 \cdot CH_2Br$ ...	~0·10M	~0·14M	63·95°	1·01
EtBr	~0·10M	~0·14M	63·95°	76·9	*n*-PrCl	~0·20M	~0·50M	95·0	3·43
n-PrBr	~0·10M	~0·14M	63·95	42·0	*iso*BuCl	~0·20M	~0·50M	95·0	0·634
*iso*BuBr ...	~0·10M	~0·14M	63·95	6·44	$CMe_3 \cdot CH_2Cl$ ...	~0·20M	~0·50M	95·0	0·159

* Cf. experimental section.

TABLE II.

Relative Rates (Et = 1) *for the Reactions of Alkyl Bromides.*

(1) = Bimolecular reaction with NaOEt in EtOH at 95°. (2) = Solvolytic reaction in "50%" H_2O–EtOH at 95°. (3) = Reaction with $AgNO_3$ in "70%" EtOH at 64.° ††

Alkyl bromide.	(1).	(2).	(3).	Alkyl bromide.	(1).	(2).	(3).
Me	15	2·0	0·81	*iso*Bu	0·41	0·080	0·084
Et	1	1	1	$CMe_3 \cdot CH_2 \cdot$	0·00001	0·0065	0·013
n-Pr	(0·28) *	0·57	0·55				

* Calculated on the assumption that the ratio $k_{EtBr}/k_{n\text{-}PrBr}$ is independent of temperature.

† The differences of rate between the three chlorides included in our investigation (Table I) are somewhat smaller (relative rates: *n*-Pr, 1; *iso*Bu, 0·18; *neo*Pentyl, 0·046) than those found for the corresponding bromides (relative rates: *n*-Pr, 1; *iso*Bu, 0·16; *neo*Pentyl, 0·025), but it should be noted that the experimental conditions were different in the two sets of experiments.

‡ A similar order of rates for part of the alkyl series (relative rates: Me, 0·43; Et, 1; *n*-Pr, 0·45; *iso*Bu, 0·063) was observed by Burke and Donnan (*loc. cit.*) for the reaction of the alkyl iodides with silver nitrate in dry ethyl alcohol at 24·5°.

The most important feature of the results (see Table II) is that the main differences of behaviour which the solvolytic reaction (this vol., p. 164) exhibits, by comparison with the bimolecular reaction with sodium ethoxide (this vol., p. 157), are now emphasised. Thus, the retarding effect of β-alkyl substitution, which was reduced on passing from the bimolecular reaction to the solvolytic process, is, on the whole, further reduced in the silver reaction, so that the *neo*pentyl halides, though still the slowest of the halides, are not notably unreactive towards silver nitrate.* Again, the effect of changing from the bimolecular to the solvolytic reaction on the relative reactivities of the methyl and ethyl halides is emphasised, so much so that the rate for methyl bromide is now reduced below that for ethyl bromide. The results are consistent with the hypothesis that, in the silver reaction, the effects which are expected to be associated with an ionisation mechanism are exerting a greater influence on the variation of rate in the series as a whole than is the case in the solvolytic reaction.

To attempt a detailed explanation of the rate relationship for the silver reaction would be unjustified in view of the complex nature of the reaction, but we suggest three reasons for the absence of the theoretical rate sequence to be expected for a simple ionisation process, namely, Me < Et < *n*-Pr < *iso*Bu < *neo*Pentyl. First, the inequality Me < Et is in fact observed, and the remaining inequalities, which should be much smaller because of the loss suffered by the inductive effect in transmission through an intervening carbon atom, may fail to appear because we work with energised molecules, not the static molecules contemplated by the simple theory which underlies a polar sequence. Secondly, owing to the heterogeneous catalysis by silver halide, there may be a facilitating effect which depends on the ease of adsorption of the halide and decreases in importance in the order Me > Et > *n*-Pr > *iso*Bu > *neo*Pentyl. Thirdly, the electrophilic catalysis by silver ions may be assisted by solvent molecules, or by nitrate ions, acting by virtue of their nucleophilic activity towards the α-carbon atom. Such an assistance would involve an adsorbed transition state of the type $[H_2O \ldots R \ldots Br \ldots Ag]^+$, and its importance would again diminish in the order Me > Et > *n*-Pr > *iso*Bu > *neo*Pentyl. For the *neo*pentyl halides, it may be safely assumed that any effect of this type would be quite negligible because of the resistance of the structure to the attack of a reagent on the α-carbon atom. The work of Whitmore, Wittle, and Popkin (*J. Amer. Chem. Soc.*, 1939, **61**, 1586) indirectly shows that the reaction involves rearrangement of the *neo*pentyl group.

EXPERIMENTAL.

Materials.—*neo*Pentyl chloride, prepared by chlorination of *neo*pentane (Whitmore and Fleming, *J. Amer. Chem. Soc.*, 1932, **54**, 3460; 1933, **55**, 3803, 4161), was fractionated through a 15-plate column (this vol., p. 159); b. p. 85·0—85·1°/760 mm. *neo*Pentyl bromide was prepared and purified as previously described. The other halides used were commercial samples which had been subjected to rigorous purification (cf. this vol., pp. 160, 163, and 165). Commercial absolute ethyl alcohol was dried (this vol., p. 160), refluxed with silver nitrate for several hours, and fractionated.

Rate Measurements.—For the experiments with the alkyl chlorides, the appropriate quantity of "AnalaR" silver nitrate was dissolved in 600 ml. of distilled water and the solution made up to 2 l., at room temperature, with purified ethyl alcohol. This reagent was used in all the comparative measurements involving the alkyl chlorides and the medium will be referred to as "70%" EtOH (B). In the experiments with the bromides, silver nitrate was dissolved in the medium ["70%" EtOH (A)] obtaining by mixing, at room temperature, 70 vols. of alcohol and 30 vols. of distilled water. In all cases, weighed quantities of the halides were made up to 100 ml. at 0° with the reagent solutions described above, and portions of 5 ml. were sealed up in tubes, which were wrapped in tin foil and immersed in the thermostat. Tubes

* This result was evident from the work of Whitmore and his co-workers (see this vol., p. 157).

were removed at intervals, and the silver nitrate content estimated either by electrometric titration with standard potassium chloride solution or by titration with ammonium thiocyanate, using ferric sulphate as indicator. The reaction is complex, but it approximates to one of the second order (cf. p. 169), and, for comparative purposes, the second-order rate coefficients were averaged. The average values obtained in all the experiments have already been recorded (Table I); these have been corrected for thermal expansion between the temperature at which the 5-ml. portions were measured and the temperature of the thermostat. The results of some typical experiments (uncorrected for expansion) are shown in Table III; k_2 is in sec.$^{-1}$ g.-mol.$^{-1}$ l.

TABLE III.

Illustrating Determination of Second-order Rate Coefficients.

I. *Alkyl bromides in* " 70% " EtOH (A) *at* 63·95°.

(i) *neo*Pentyl bromide. [RBr] and [$AgNO_3$] expressed in ml. of 0·03N-KCl per 5 ml. of solution.

t (hrs.) ...	0	1	3	5	10	11·3	18	21·5
[RBr] ...	15·74	15·05	13·59	12·60	10·50	9·98	8·21	7·43
[$AgNO_3$]	23·52	22·83	21·37	20·38	18·28	17·76	15·99	15·21
$k_2 \times 10^5$	—	9·72	10·23	9·53	9·16	9·31	8·86	8·84

(ii) *iso*Butyl bromide. [RBr] and [$AgNO_3$] expressed in ml. of 0·03N-KCl per 5 ml. of solution.

t (mins.)	0	9	18	30	42	57·5	72	81	99	120	135	156
[RBr] ...	15·68	15·07	14·35	13·57	12·95	12·18	11·37	11·05	10·42	9·71	9·19	8·71
[$AgNO_3$]	22·31	21·70	20·98	20·20	19·58	18·81	18·00	17·68	17·05	16·34	15·82	15·34
$k_2 \times 10^4$	—	5·59	6·34	6·32	6·06	5·99	6·23	6·09	5·93	5·87	5·93	5·78

(iii) Ethyl bromide. [RBr] and [$AgNO_3$] expressed in ml. of 0·0306M-ammonium thiocyanate per 5 ml. of reaction mixture.

t (mins.)	0	3	6	8·5	11	15	21	25	30	47	56
[RBr] ...	10·76	9·20	7·87	7·23	6·68	5·50	4·57	3·90	3·33	2·06	1·65
[$AgNO_3$]	19·56	18·00	16·67	16·03	15·48	14·30	13·37	12·70	12·13	10·86	10·45
$k_2 \times 10^3$	—	7·62	7·86	7·23	6·83	7·38	7·00	7·23	7·19	7·05	6·90

II. neo*Pentyl chloride in* 70% EtOH (B) *at* 95·0°.

[RBr] and [$AgNO_3$] expressed in ml. of 0·0734N-ammonium thiocyanate per 5 ml. of solution.

t (hrs.) ...	0	4	6	7	8	10	11·25	11·75	15	16	18	18·5
[RBr] ...	12·33	11·14	10·29	10·29	10·09	9·49	9·39	9·19	8·73	8·76	8·22	8·14
[$AgNO_3$]	33·64	32·45	31·60	31·60	31·40	30·80	30·70	30·50	30·04	30·07	29·53	29·45
$k_2 \times 10^5$	—	1·46	1·76	1·51	1·47	1·54	1·41	1·48	1·37	1·28	1·36	1·36

t (hrs.) ...	20	22	23
[RBr] ...	7·86	7·20	7·20
[$AgNO_3$]	29·17	28·50	28·50
$k_2 \times 10^5$	1·37	1·50	1·44

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[*Received, August 28th*, 1945.]

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49. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXXI. The Rôle of Steric Hindrance. (Section F) A Comparison of the Rates of Reaction of Methyl, Ethyl,* n-*Propyl, and* neo*Pentyl Bromides with Wet Formic Acid.*

By I. DOSTROVSKY and E. D. HUGHES.

A comparison of the rates of reaction of the four halides named in the title with slightly aqueous formic acid gave the sequence Et>Me~*n*-Pr~*neo*Pentyl, the relative rates being Me 0·64, Et, 1·0, *n*-Pr 0·69, *neo*Pentyl 0·57. Since the *neo*pentyl reaction undoubtedly pursues the unimolecular mechanism (see Abstracts, pp. 164 and 166), the evidence of the rates suggests that this form of reaction is also important for the other halides under these conditions. However, the rate sequence is not the theoretical one for the inductive effect in the unimolecular mechanism, Me<Et<*n*-Pr<*neo*Pentyl: the main inequality Me<Et is, indeed, in the direction of the observed rate difference, but the other inequalities, which should be smaller, are not reflected in the data. This may mean that the use of formic acid has greatly diminished, but not eradicated, the bimolecular mechanism, which enters as a complicating influence into the reactions of the first three members of the series; or it may be due merely to the finite heat contents of the interacting species.

THE study of the solvolytic reactions of the primary halides in aqueous ethyl alcohol (Part XXVIII, this vol., p. 164) failed to fulfil one of the main objects of our investigations, namely, to obtain a comparison of unimolecular reaction rates for a series of primary halides. This paper records an attempt to secure such a comparison.

In aqueous ethyl alcohol, the reaction of *neo*pentyl bromide undoubtedly followed a unimolecular mechanism (this vol., p. 166), but the other halides, named in the title, reacted mainly by the alternative bimolecular route. In order to minimise the incursion of a bimolecular reaction, it is advisable to decrease the concentration of the nucleophilic reagent (*e.g.*, water or alcohol) and to employ a good ionising medium (Hughes and Ingold, J., 1935, 244 and later papers). We therefore examined the reaction with a comparatively small concentration

of water in formic acid solution, conditions which, in the case of the methyl and ethyl halides, had previously been shown to be favourable to the unimolecular mechanism (Bateman and Hughes, J., 1940, 945).

The first-order rate constants for the reactions of the four halides in "Kahlbaum" formic acid (which contains about 0·5% of water) are recorded in Table I; the constants for the reactions in aqueous ethyl alcohol are included for comparison. In both cases, the temperature was 95°, and k_1 is in sec.$^{-1}$.

TABLE I.

Comparison of First-order Rate Coefficients for the Reactions of Alkyl Bromides with 50% Aqueous Ethyl Alcohol and with "Kahlbaum" Formic Acid.

Alkyl bromide	Me.	Et.	*n*-Pr.	*neo*Pentyl.
10^6k_1 for (1) the reaction with 50% H_2O–EtOH	286	141	80·3	0·910
10^6k_1 for (2) the reaction with "Kahlbaum" formic acid	1·74	2·70	1·85	1·53

We first note that for *neo*pentyl bromide the rate is slightly greater in formic acid than in 50% aqueous ethyl alcohol. This fact recalls the similar behaviour of *tert.*-butyl chloride (Bateman and Hughes, J., 1940, 941), and may be regarded as further evidence in favour of our view that in both media the reaction of the primary halide, like that of the tertiary compound (for which the mechanism is well established), depends essentially on a rate-determining ionisation. Doubtless, the reaction in formic acid leads to the rearrangement of the *neo*pentyl structure (cf. this vol., p. 166); though this has not been experimentally proved. In the case of the other three bromides, the rates in "Kahlbaum" formic acid are much smaller than those in aqueous ethyl alcohol, and this is consistent with our previous conclusion that the reactions of these halides in the latter medium are largely bimolecular (this vol., p. 164).

The chief point which emerges from the results of Table I is that in "Kahlbaum" formic acid the reactivity of *neo*pentyl bromide is of the same order of magnitude as that of the other halides. Since the *neo*pentyl reaction must be unimolecular, the evidence of the rates suggests that the reactions of the other alkyl halides largely pursue this mechanism. The main difference, Me<Et, to be expected on account of the inductive effect, is in the observed direction. The other theoretical differences, Et<*n*-Pr<*neo*Pentyl, which should be much smaller, are the reverse of the observed differences. This may mean that the finer theoretical differences become modified from what they would be if we could work with less energised molecules, *i.e.*, closer to the absolute zero of temperature. It is an equally reasonable interpretation, however, that even in formic acid, the bimolecular contribution to the rate, which by itself would lead to the sequence Me>Et>*n*-Pr>*neo*Pentyl, is by no means negligible in the case of the first three compounds (cf. Bateman and Hughes, J., 1940, 946). It could then be concluded that the rates for a reaction which is entirely and uniformly unimolecular throughout the series will exhibit the theoretical sequence (S_N1:—Me<Et<*n*-Pr<*neo*pentyl) to be expected from the operation of the inductive effects of the alkyl groups; but that, owing to the great tendency for the incursion of a bimolecular contribution to the reaction rate in the simpler structures, it is difficult to test the validity of this conclusion. Some confirmation for the view that an alkyl halide containing a "*neo*pentyl" structure may exhibit quite normal reactivity in unimolecular reactions is, however, provided by available data for the rates of solvolysis of three tertiary halides, one of which is a substituted *neo*pentyl compound, under comparable experimental conditions. These are contained in Table II.

TABLE II.

First-order Rate Constants for the Solvolysis of Tertiary Alkyl Halides in 80% Aqueous Ethyl Alcohol at 25°.

Alkyl chloride	*tert.*-Butyl (CH_3·CMe_2Cl).	*tert.*-Amyl (CH_3·CH_2·CMe_2Cl).	*aa*-Diethyl*neo*pentyl (CMe_3·CEt_2Cl).
10^5k_1 (sec.$^{-1}$)	0·854 *	1·50 †	11·7 ‡

* Cooper, Hughes, and Ingold, J., 1937, 1280.
† Hughes and MacNulty, J., 1937, 1283.
‡ Bartlett and Knox, *J. Amer. Chem. Soc.*, 1939, **61**, 3184.

In the tertiary halides, the ionisation mechanism is well developed and easy to isolate from accompanying bimolecular substitution, and it is clear that the "*neo*pentyl" structure in the last compound has not introduced any abnormality in its reactivity towards unimolecular solvolysis. A further discussion of the results herein recorded is contained in the following paper.

EXPERIMENTAL.

Materials.—The quality of the halides used was the same as in the foregoing papers.

Kinetic Measurements.—A weighed quantity of the halide was dissolved in "Kahlbaum" formic acid (which contained about 0·5% of water), and the solution made up to a definite volume at room temperature. Portions of 5 ml. were then enclosed in small sealed tubes, which were heated for known times in the thermostat (at 95·15°±0·01°), cooled in solid carbon dioxide–alcohol, and their halide-ion contents estimated electrometrically. Owing to the slight decomposition of the formic acid which causes pressure in the reaction tubes, it was not possible to proceed with the runs for more than about 15 hours (*ca.* 5—10% reaction); nevertheless, it was possible to measure the initial rates quite accurately. The observations are adequately summarised in Table I; the results of two typical experiments are recorded in detail in Table III, where k_1 is in sec.$^{-1}$.

TABLE III.

Illustrating Determination of First-order Rate Constants.

([RBr] expressed in equivalent ml. of 0·01N-$AgNO_3$ per 5 ml. of reaction mixture.)

1. n-*Propyl bromide.*

t (hrs.)	0	1	2	4	5	6	7	8
[RBr]	51·94	51·57	51·21	50·55	50·27	49·94	49·70	49·36
$k_1 \times 10^6$	—	1·98	1·95	1·89	1·82	1·81	1·75	1·78

Mean $k_1 = 1·85 \times 10^{-6}$. A duplicate run gave $k_1 = 1·84 \times 10^{-6}$.

2. neo*Pentyl bromide.*

t (hrs.)	0	1	3	6	9	13	17·5
[RBr]	55·17	54·87	54·23	53·35	52·50	51·52	50·19
$k_1 \times 10^6$	—	1·47	1·60	1·56	1·53	1·46	1·51

Mean $k_1 = 1·52 \times 10^{-6}$. A duplicate run gave $k_1 = 1·54 \times 10^{-6}$.

We wish to acknowledge with gratitude our indebtedness to Professor C. K. Ingold, F.R.S., for his interest in the work described in this and preceding papers.

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[*Received, August 28th,* 1945.]

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50. *Mechanism of Substitution at a Saturated Carbon Atom. Part XXXII. The Rôle of Steric Hindrance. (Section G) Magnitude of Steric Effects, Range of Occurrence of Steric and Polar Effects, and Place of the Wagner Rearrangement in Nucleophilic Substitution and Elimination.*

By I. DOSTROVSKY, E. D. HUGHES, and C. K. INGOLD.

This abstract is intended to render intelligible any of the three main divisions, (*A*), (*B*), and (*C*), of the paper without the need of reading the others.

Discussion starts from the following facts and conclusions derived from the preceding six papers. Whitmore had shown qualitatively that the *neo*pentyl halides are singularly unreactive to certain substituting agents. It has now been established that this behaviour is special to bimolecular nucleophilic substitution (S_N2); and that a measure of it is that for *neo*pentyl bromide rates are reduced, as compared with lower primary bromides, by factors of about 10^5, and activation energies are increased by about 6 kg.-cals. It is also proved that in unimolecular nucleophilic substitution (S_N1) the reactivity of *neo*pentyl halides is comparable with that of the other primary alkyl halides. Finally it is shown that, whilst in bimolecular substitutions the form of the *neo*pentyl group is preserved, in unimolecular substitution the group becomes converted into a *tert.*-amyl group, and, in the accompanying unimolecular elimination, into *iso*amylene.

(*A*, p. 175). A semi-quantitative theoretical treatment of steric hindrance in bimolecular nucleophilic substitution is given as a development of the transition state theory of reaction rate. It is possible to calculate the steric increment of activation energy in certain cases, and an upper limit to this increment in other cases. The calculations show clearly how the apparently peculiar position of *neo*pentyl compounds arises, puts their behaviour in perspective with that of other alkyl compounds, and leaves no doubt that the observed rate and energy effects are of steric origin. It is shown, *e.g.*, that steric effects in bimolecular nucleophilic substitution of *tert.*-butyl halides are relatively small; and it is explained why the effect of an inserted methylene group, as revealed by comparison of *tert.*-butyl with the homologous *neo*pentyl halides, is qualitatively opposite to the effect shown by comparison of ortho-substituted benzoic acids with the homologous phenylacetic acids in relation to Victor Meyer's classical experiments on steric hindrance in esterification.

(*B*, p. 186). Our general picture of bimolecular and unimolecular substitutions and eliminations is broadened by these conclusions. It is perceived that much of the evidence formerly held to support the Thorpe–Ingold valency deflexion hypothesis can be consistently explained as an effect of steric hindrance. Surveying, in other fields, the evidence of reaction rates in the light of our more sharply defined views on steric hindrance, we find confirmation of those mechanisms for the conversion of alcohols into halides, which had earlier been inferred only from evidence on the Walden inversion; we find confirmation also of various other previously assumed mechanisms, including the mechanisms of carboxyl esterification and hydrolysis. Polar and steric effects are in general superposed in bimolecular substitutions. The two effects jointly determine the bimolecular nucleophilic rate sequence Me > Et > Pr$^\beta$. There is no discernible steric effect in unimolecular substitution. Consequently, for structures which are sterically hindered in bimolecular substitution, more success may sometimes be achieved in effecting reaction by the addition of an ionising solvent (*e.g.*, water) than by the introduction of powerfully nucleophilic reagents (*e.g.*, hydroxide ion). Polar effects are responsible for the increasing rate of ionisation in the series primary, secondary, tertiary, alkyl halides, a measure of which is the rate factor of about 10^8 between primary and tertiary bromides, and an activation energy difference of about 7 kg.-cals. Our view with regard to the proportions in which bimolecular and unimolecular mechanisms are superposed in the aqueous or alcoholic solvolysis of secondary alkyl halides is adjusted in the sense implying that the racemisation accompanying their unimolecular solvolysis is more nearly complete than we used to believe.

(*C*, p. 192). The Wagner and related rearrangements in the major field of heterolytic substitutions used to be classified with 1 : 3-eliminations, but it is now clear that they belong to unimolecular nucleophilic processes, either of substitution or elimination (S_N1 or $E1$). This type of mechanism is a necessary condition for rearrangement, but not a sufficient condition. Rearrangement depends otherwise, in an intelligible way, on resonance energy due to conjugation and hyperconjugation in the carbonium ion. Shoppee's rule for relative migratory

aptitudes can be understood. In one case it can be proved that rearrangement follows, and does not accompany, the ionisation which is necessary for it. The Wagner rearrangement may also occur in unimolecular homolytic reactions, which involve the formation of an intermediate free radical, instead of a carbonium ion.

THIS group of papers, Parts XXVI—XXXII, marks a new departure in the research to which it contributes, the general plan of which was set out in Part V (J., 1935, 244). Our concern has been (*a*) to classify substitutions, particularly nucleophilic substitutions, at a saturated carbon atom according to their polar type, (*b*) to establish the mechanisms, in particular the bimolecular and unimolecular mechanisms, of such substitutions, and (*c*), for each class of substitution, to examine constitutional and solvent effects on the mechanism, velocity, and spatial orientation of reaction. Objects (*a*) and (*b*) have been largely accomplished, whilst (*c*) is being actively pursued. However, in the discussions of constitutional effects published hitherto,* we have given attention almost entirely to polar influences, and hardly at all to steric effects. Indeed, the suggestion has been made that we have neglected steric effects, though it should have been clear from our reference to them in Part V that we have simply been putting first things first. Our view was, and is, that polar effects determine all the broad phenomena, while steric hindrance makes only quantitative differences in general, though it can create qualitatively special situations in particular cases.† However, a more detailed description of the effects of steric hindrance is obviously necessary to a general statement of the theory, and we now take the first steps in this direction, even though our work on the polar effect is still far from finished. The main conclusions set out in this paper, as well as the more important of the experimental data given in the accompanying papers, were reported in summary by one of us in 1941 (Hughes, *Trans. Faraday Soc.*, **37**, 620).

The idea of steric hindrance, as a factor reducing reaction rate, originated in the last century, and is the subject of an extensive literature, which we shall not here summarise, since other reviews are available. But inasmuch as the steric concept has usually been applied simply to the molecular models of reactants, it has not hitherto been employed in a form capable in principle of quantitative development. For the transition state theory teaches that, in the discussion of effects on reaction rate, the transition state and the initial state must be treated differentially; and it is obvious that, in relation to steric hindrance, the most important part of any such differential treatment may well be the discussion, not of the initial state of the reactants, but of the transition state, in which a larger number of atoms may have to be brought into a particular stereochemical relation with one another than in the initial state. It is inherent in this point of view that steric hindrance should not be associated, as it so often is by implication if not explicitly, with a particular reactant, or a particular over-all chemical reaction: rather it is a property of a particular reaction mechanism. It follows also that the steric hindrance associated with a particular mechanism cannot usefully be discussed unless the mechanism itself has been studied at least to a point such that the composition and approximate configuration of the transition state is known. However, our work on nucleophilic substitution at saturated carbon atoms seems to have reached a stage at which this preliminary condition is fulfilled.

The problem of steric hindrance being essentially quantitative, its complete treatment in relation to any particular mechanism of reaction requires, in principle, a quantitative knowledge of (*a*) the configuration of the transition state, and (*b*) its internal force system. Even in the most favourable cases our existing knowledge of these geometrical and dynamical particulars is not very accurate or complete. This is especially true of the force system. Therefore we thought it advisable to commence the study of steric hindrance in nucleophilic substitution, not with an average or typical case of this nearly universal phenomenon, but with an extreme case, in which the steric effect produces such a qualitatively striking situation that quantitative precision in the theoretical treatment is not necessary to a demonstration. Though relieved in this way of the need to face the difficulties of an exact calculation, we do include a semi-quantitative treatment in the present discussion.

Our attention was directed to the *neo*pentyl halides, as possibly providing an extreme example of steric hindrance, by Whitmore's statements about these substances: he discovered (see Part XXVI) their remarkable inactivity towards powerfully nucleophilic substituting agents, such as hydroxide or ethoxide ions. In the accompanying papers (Parts XXVI—XXXI) these observations are placed in perspective by quantitative comparisons of the rate of nucleophilic substitution of *neo*pentyl and of other simple, primary alkyl halides. It is a notable outcome of this work that the striking lack of reactivity of *neo*pentyl halides is particularly characteristic of the bimolecular mechanism of nucleophilic substitution (S_N2). However, even in reactions by this mechanism, these halides are not absolutely inactive, the rates of bimolecular substitution of *neo*pentyl bromide, for example, with ethoxide or iodide ions being merely some 10^4—10^6 times smaller than for the other primary alkyl bromides which have been studied under similar physical conditions. The general character of the evidence is indicated by the data in Table I, taken from Parts XXVI and XXVII, for relative rates of substitution of the various alkyl halides, and for the corresponding Arrhenius activation energies. It has been pointed out how the successive replacement by methyl groups of the three β-hydrogen atoms of the ethyl group causes a fall of rate which steepens rapidly as the third methyl is introduced. It has also been noted that the changes of rate are largely accounted for by changes in the apparent energy of activation.

* Since 1933; but some of the relevant papers appear under serial titles other than that here used, *e.g.*, "Reaction Kinetics and the Walden Inversion," and "Criterion for the Mechanism of the Reactions of Alkyl Halides with Hydroxylic Solvents."

† "We envisage the operation of steric hindrance, *i.e.*, repulsions due to the interpenetration of atomic electron clouds at very small distances: such effects are quantitatively important, though they seldom seem to alter the direction of the broader distinctions. . . ." (Part V, *ibid.*, p. 246).

TABLE I.

Relative Rates and Arrhenius Activation Energies of Bimolecular Substitutions of Primary Alkyl Bromides.

	Methyl.	Ethyl.	*n*-Propyl.	*iso*Butyl.	*neo*Pentyl.
Substitution by OEt^- *in* EtOH					
Relative rates at 55°	17·6	1	0·28	0·030	0·0000042
E (kg.-cals.)	20·0	21·0	—	22·8	26·2
Substitution by I^- *in* $COMe_2$					
Relative rates at 64°	—	1	—	—	0·000053
E (kg.-cals.)	—	19	—	—	25

We shall now endeavour to show that the interpretation, as an effect of steric hindrance, of the low rates and high activation energies obtained for the reactions of *neo*pentyl bromide, indeed, that the whole set of phenomena illustrated in Table I, is consistent with what is known concerning the geometrical and dynamical factors which affect the bimolecular mechanism of substitution (S_N2).

(A) *Discussion of Steric Effects in Bimolecular Nucleophilic Substitutions of Alkyl Compounds, particularly of Alkyl Halides.*

(a) *Geometrical Factors.*—In principle the initial and transition states of reaction have to be treated differentially, though the more important part of the present considerations relates to the transition state. As to the geometry of the "model" of the alkyl compound in its initial state, we assume bond lengths corresponding to summed covalent radii, and carbon bond angles equal to the tetrahedral angle. All single bonds are assumed to be without any internal resistance to torsional movement. The data employed are collected in Table II, and are substantially as recorded by Pauling ("Nature of the Chemical Bond," Cornell Press, 1940), though the lower lines of figures require some further explanation, to be given later (p. 177).

TABLE II.

Atomic Dimensions (A.) *used in Evaluation of Steric Effects in Bimolecular Substitutions of Alkyl Halides.*

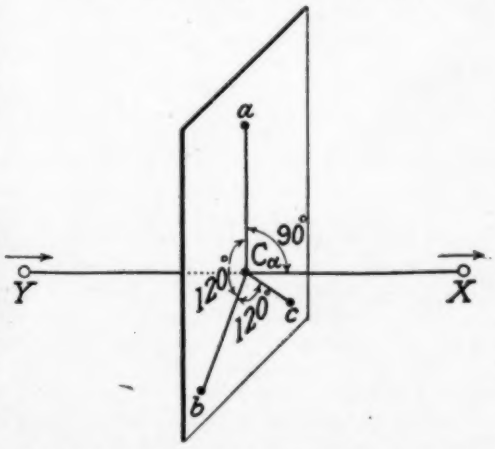
	H.	C.	Cl.	Br.	I.
Covalent radius (ρ_{co})	0·32	0·77	0·99	1·14	1·33
Univalent ionic (crystal) radius (ρ_{ion})	—	—	1·81	1·95	2·16
Maximal van der Waals radius ($\rho_{max.}$)	1·2	1·6	1·8	1·95	2·15

It is generally agreed that, in the transition state of a bimolecular nucleophilic substitution, the nuclei of the substituting atom Y, of the carbon atom C_α at which the substitution takes place, and of the displaced atom X, are collinearly arranged, whilst the nuclei of the other atoms, *a*, *b*, and *c*, to which C_α is covalently bound lie in directions from C_α inclined at angles of 120° to one another, and in a plane which passes through C_α, and is perpendicular to the line of Y and X (Fig. 1). This statement refers to the "model" of the transition state, *i.e.*, to its equilibrium configuration with respect to all those normal co-ordinates which are associated with minima of potential energy. The statement is to be regarded as exact only for certain special cases, *e.g.*, for a "symmetrical" substitution,* such as

$$Br^- + CH_3{-}Br \longrightarrow Br{-}CH_3 + Br^-.$$

FIG. 1.

Fundamental model of the transition state in bimolecular nucleophilic substitution.



It is only an approximate description of the model of the transition state in more general cases, because it neglects such deviations as may arise from steric hindrance itself. However, such deviations will almost always be relatively small: the nuclei of Y, C_α, and X will at least lie near a straight line, and the nuclei of *a*, *b*, *c*, and C_α near a plane perpendicular to the line. The theoretical argument in favour of this type of model is that it minimises repulsive energy in the transition state; and experimentally the model has been well established by kinetic investigations relating to the Walden inversion (for a summary, see Cowdrey, Hughes, Ingold, Masterman, and Scott., J., 1937, 1252; and Hughes, *Trans. Faraday Soc.*, 1938, **34**, 186).

Since our purpose is to examine steric effects, we shall be justified in using the idealised model of the transition state, and in regarding the determination of any allowances necessary for deviations of steric origin from this model as part of the problem to be solved. With the idealised model as basis, we can calculate the distances between the nuclei of the attacking and displaced atoms and those of all the other atoms of the structure.

* The term is applied by Polanyi to substitutions in which the introduced and expelled groups are identical. We use it in this way without implications respecting mechanism.

A consideration of these distances provides an estimate of the relative importance of the steric factor in different structures. In a second stage of the argument the steric effects associated with the different distances have to be evaluated in terms of energy, and it is at this stage that any deviations from the idealised model which would reduce the total energy should be taken into account.

The model of the transition state, as described up to this point, fixes the directions of the bonds of C_α. The bonds of all other carbon atoms are assumed to make angles equal to the tetrahedral angle. All single bonds are assumed to have a normal length, corresponding to summed covalent radii (Table II), and to be devoid of internal resistance to torsional movement. The lengths of the partial, and partially ionic, bonds, YC_α and $C_\alpha X$, require to be specially estimated. Because of the difficulty of at once making a precise estimate, we shall start with an arbitrary approximation, being prepared later to correct it if necessary, after calculation of a closer approximation. For the present, we estimate YC_α and $C_\alpha X$ by adding the covalent radius of carbon to the mean of the covalent and negative ionic radii of Y or X (Table II).* This procedure differs, it should be remarked, from that of Baughan and Polanyi (*Trans. Faraday Soc.*, 1941, **37**, 648), who take the full negative ionic radii of Y and X, though only one unit of charge is shared between them. Furthermore, they employ gaseous ionic radii, whilst we prefer the well-established crystal radii, believing that the condition of an ion in a crystal is a better approximation than that in a gas to its condition in a dipolar solvent, since the heats of solution of ionic crystals in polar solvents are so very much less than their heats of sublimation (a few kg.-cals. at most, as against about 50 kg.-cals. for univalent crystals). Our distances, YC_α and $C_\alpha X$, for the transition state are accordingly considerably shorter than theirs: in the example BrC_α, the smaller value for the distance is supported by the closer approximation calculated later (p. 184).

The particulars given fix the stable positions of those atoms, the α-hydrogen and β-carbon atoms, which are directly bonded to C_α: their positions are in fact completely determined by the bonding forces. By contrast, the stable positions of those atoms which are linked through one intermediate carbon atom to C_α, *viz.*, the β-hydrogen and γ-carbon atoms, are left indeterminate in one degree of freedom by the bonding forces, because these forces provide no resistance to rotation round the C_α–C_β bond. The disposition of the atoms with respect to rotation about this bond must therefore be determined by the non-bonding forces. Between any pair of atoms which are not bonded to each other, these forces consist of van der Waals attractive, and steric repulsive, forces; which balance, with minimisation of the non-bonding energy, when the internuclear distance has a value called the van der Waals distance. In general, the bonding forces make it impossible to secure an orientation about the C_α–C_β bond which will simultaneously equate to the van der Waals distances all the non-bonded internuclear distances in which the β-hydrogen and γ-carbon atoms are concerned. However, the condition determining the actual orientation is evidently that the total non-bonding energy shall be a minimum. This condition might appear difficult to use for purposes of calculation, but in fact it is not in the cases in which we are interested; for when there is any appreciable steric hindrance involving a β-hydrogen or γ-carbon atom, *i.e.*, if the bonding forces restrict any non-bonded internuclear distance involving any of these atoms to values substantially less than the van der Waals distance, then the general condition almost always reduces to the following, namely, that the orientation of the group will be so determined that the non-bonded internuclear distance which falls furthest below the corresponding van der Waals distance will be a maximum. This follows because, whilst van der Waals attractive energy varies relatively slowly with distance, steric repulsive energy increases with diminishing distance according to a curve which steepens exceedingly rapidly at distances substantially smaller than the van der Waals distance. Obviously it will be the particular internuclear distance which falls on the steepest part of the energy curve which will determine the direction of the forces tending to adjust orientation when the group of atoms affected by rotation about the C_α–C_β bond is out of equilibrium with respect to non-bonding energy. When no non-bonded distance is restricted to such small values, the simplified condition for minimal energy will not necessarily apply; but we shall not worry, because in this case the atoms concerned will not contribute appreciably to the steric effect.

The position of a γ-carbon atom being determined according to these principles, a similar series of statements will apply to the γ-hydrogen and δ-carbon atoms, whose disposition with respect to rotation about the C_β–C_γ bond is left indefinite by the bonding forces, and must again be determined so as to minimise the non-bonding energy. Similar principles apply to the still more remote atoms.

We now enter into some detail with respect to the relatively simple case of a symmetrical substitution, taking as example the displacement of bromine as bromide ion from an alkyl bromide by means of an attacking bromide ion. This type of displacement has been experimentally studied by Hughes, Juliusberger, Scott, Topley, and Weiss by the use of radio-active bromine, as well as by methods dependent on optical activity (J., 1936, 1173); and also by Sugden and his collaborators using radio-bromine (J., 1939, 1279, 1836; 1945, 586).

The alkyl groups to be compared with respect to the steric effects exerted in this and similar substitutions are selected in order to show the influence of successive α- and β-methyl substitution:

methyl	ethyl	*iso*propyl	*tert.*-butyl	..... (α-methylated series)
ethyl	*n*-propyl	*iso*butyl	*neo*pentyl	..... (β-methylated series)

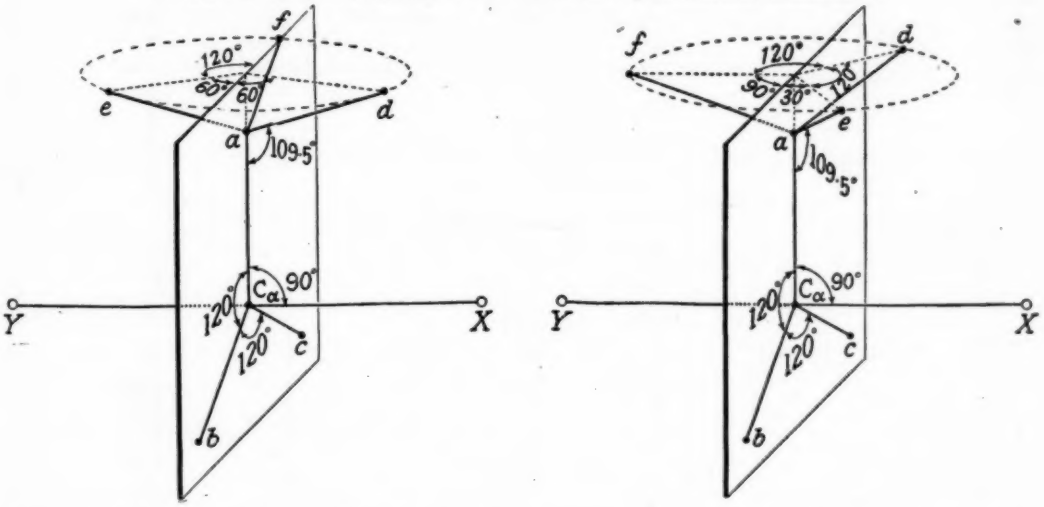
The arrangement of most of these groups in the transition state of substitution can be followed with the

* The approximation formula, three-quarters of the $C_\alpha X$ bond length plus one-quarter of the C_α-to-X van der Waals distance (which is suggested by known relations between bond length and bond order), gives the same results.

aid of Fig. 2*a*. For the methyl group, *a*, *b*, and *c* represent three hydrogen atoms. In the ethyl group *a* becomes the β-carbon atom, whilst *d*, *e*, and *f* are the three β-hydrogen atoms; they are so oriented with respect to rotation about the C_α–C_β bond that the planes *da*C_α and *ea*C_α are each inclined at 60° to the plane *bc*C_α*af*. In *iso*propyl, *b* also becomes a β-carbon atom, and the three β-hydrogen atoms it carries are similarly oriented with respect to rotation about their C_α–C_β bond. In *tert.*-butyl, *c* becomes yet another β-carbon atom, carrying three β-hydrogen atoms analogously oriented.

FIG. 2*a*. FIG. 2*b*.

Configurations of alkyl groups in transition states of bimolecular substitution.



In the case of the *n*-propyl group, *b* and *c* are α-hydrogen atoms, *a* is the β-carbon atom, *d* and *e* are the β-hydrogen atoms, and *f* is the γ-carbon atom. The γ-hydrogen atoms are not indicated in the diagram, and, as none of them produces any steric effect, it is not necessary to consider their precise positions. However, as a step towards showing that they in fact yield no steric effect, we imagine them to be arranged as they would be if they did produce one: denoting them by *g*, *h*, and *i*, we find that the planes *gfa* and *hfa* will make angles of 60° with the plane *bc*C_α*afi*.

The case of the *iso*butyl group requires reference to Fig. 2*b*. Here *b* and *c* are the α-hydrogen atoms, *a* is the β-carbon atom, *f* is the β-hydrogen atom, and *d* and *e* are the γ-carbon atoms. The planes *da*C_α and *ea*C_α are each inclined at 30° to the plane *bc*C_α*a*; whilst the plane *fa*C_α is perpendicular to the plane *bc*C_α*a*, and contains the atoms Y and X. The γ-hydrogen atoms are not shown. The three γ-hydrogen atoms, *g*, *h*, and *i*, attached to the γ-carbon atom *d*, are so oriented with respect to rotation about the *a*–*d* bond that atom *i* is the most remote of the three from X, whilst *g* and *h* are equidistant from X. Similarly the γ-hydrogen atoms, *j*, *k*, and *l*, attached to *e* are oriented about the *a*–*e* bond so that *l* is the most remote from X, whilst *j* and *k* are equidistant from X.

The arrangement of the *neo*pentyl group can be illustrated by Fig. 2*a*. In this case *b* and *c* are the α-hydrogen atoms, *a* is the β-carbon atom, and *d*, *e*, and *f* are the three γ-carbon atoms. The three γ-hydrogen atoms, *g*, *h*, and *i*, attached to *d* are so oriented by rotation round the *a*–*d* bond that atom *i* is the most remote from X, whilst *g* and *h* are equidistant from X. The γ-hydrogen atoms, *j*, *k*, and *l*, attached to *e* are oriented about the *a*–*e* bond so that *l* is the most remote from Y, whilst *j* and *k* are equidistant from Y. The three γ-hydrogen atoms attached to *f* may be imagined to be arranged like the three γ-hydrogen atoms of the *n*-propyl group: they do not contribute to the steric effect.

Table III contains the distances calculated for the models described, between the nuclei of the bromine atoms and those of the carbon and hydrogen atoms of the alkyl groups, first for the initial states, and then for the transition states, of the bromine exchange reactions under discussion. The table also contains a note of the numbers of carbon or hydrogen atoms situated at these distances from the bromine atoms, as well as of the numbers of identical distances (which may be greater, where, in the transition state, carbon or hydrogen atoms are situated on a plane of symmetry between the two bromine atoms). When several different distances exist in an alkyl group between atoms of the same kind and classification, we give only the smallest such distance, because in no case does any omitted longer distance give rise to a notable steric effect. The numbers of these omitted distances can readily be deduced from the numbers of stated distances, since the total number of distances, stated plus omitted, is obviously equal to the number of like carbon or hydrogen atoms in the initial state, and equal to twice that number in the transition state.

It is necessary to compare these distances (" model distances ") with the distances below which compression would occur (" touching distances "). The latter, the van der Waals distances between the different pairs of

TABLE III.

Model Distances between the Nuclei of the Bromine Atoms and those of the Carbon and Hydrogen Atoms in the Initial and Transition States of the Substitution $Br^- + RBr \longrightarrow BrR + Br^-$.

Key.—r = Distance (in A.), n = number of C or H atoms at the stated distance from Br atoms, N = number of occurrences of the stated distance.

Group R.		CH_3.	$MeCH_2$.	Me_2CH.	Me_3C.	$MeCH_2{\cdot}CH_3$.	$Me_2CH{\cdot}CH_3$.	$Me_3C{\cdot}CH_3$.
				Initial state.				
$H_\alpha \ldots Br$	r	2·50	2·50	2·50	—	2·50	2·50	2·50
	$n = N$	3	2	1	—	2	2	2
$C_\beta \ldots Br$	r	—	2·81	2·81	2·81	2·81	2·81	2·81
	$n = N$	—	1	2	3	1	1	1
$H_\beta \ldots Br$	r	—	2·98	2·98	2·98	2·98	2·98	—
	$n = N$	—	2	4	6	2	1	—
$C_\gamma \ldots Br$	r	—	—	—	—	4·22	3·16	3·16
	$n = N$	—	—	—	—	1	1	2
$H_\gamma \ldots Br$	r	—	—	—	—	4·53	3·05	3·05
	$n = N$	—	—	—	—	2	2	4
				Transition state.				
$H_\alpha \ldots Br$	r	2·55	2·55	2·55	—	2·55	2·55	2·55
	n	3	2	1	—	2	2	2
	N	6	4	2	—	4	4	4
$C_\beta \ldots Br$	r	—	2·78	2·78	2·78	2·78	2·78	2·78
	n	—	1	2	3	1	1	1
	N	—	2	4	6	2	2	2
$H_\beta \ldots Br$	r	—	2·43	2·43	2·43	2·43	2·30	—
	n	—	2	4	6	2	1	—
	N	—	2	4	6	2	1	—
$C_\gamma \ldots Br$	r	—	—	—	—	3·41	2·88	2·42
	n	—	—	—	—	1	2	2
	N	—	—	—	—	2	2	2
$H_\gamma \ldots Br$	r	—	—	—	—	2·99	2·71	2·15
	n	—	—	—	—	2	4	4
	N	—	—	—	—	2	4	4

atoms, are obtained by the summation of appropriately determined van der Waals radii. Table II contains a list of what we call *maximal* van der Waals radii, the figures, except for carbon, being those given by Pauling as van der Waals radii (*op. cit.*). The value for carbon is estimated by adding 0·8 A. to the covalent radius, since the maximal van der Waals radii for all atoms for which directly determined values exist are about this amount greater than the corresponding covalent radii. Reference to the significance of the value for carbon is made below.

These radii are here called " maximal " because, as Pauling has noted, smaller radii are effective for directions making moderate or small angles with the direction of a covalency (*loc. cit.*). This is shown by the properties and dimensions of molecules such as carbon tetrachloride and methylene chloride, in which the chlorine–chlorine distance is considerably less than twice the maximal van der Waals radius of chlorine. Our knowledge of the variation of the effective van der Waals radius with angular separation from a covalency direction is at present very meagre: support can be adduced for the assumption of a shortening (from the maximum radius) of about 0·8 A. for angular separations approaching zero, and a shortening of zero for angular separations of about 90° or greater; whilst Pauling estimates that for an angular separation of 35° the shortening is about 0·5 A. These figures seem to be largely independent of the nature of the atom. If we suppose that, as the angular separation rises from 0° to 90° the shortening of the radius drops from 0·8 A. to zero as a cosine curve drops from its maximum to its minimum, the shortening for an angle of 35° would be 0·53 A., in satisfactory agreement with Pauling's estimate. Arbitrarily, we assume a relation of this form:

$$\rho_{max.} - \rho_\theta = 0{\cdot}4(1 + \cos 2\theta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $\rho_{max.}$ is the maximal, and ρ_θ the effective, van der Waals radius (in A.), and θ ($<90°$) is the angular separation from a covalency. In a polycovalent atom a given direction may lie within 90° of more than one covalency, and when this is so, the smallest angular separation is considered to determine the shortening of the radius. In the case of carbon the maximal van der Waals radius, estimated as 1·6 A. in Table II, will be greater than the effective radius in any actual direction, since in this atom all directions lie within 70° of at least one covalency.

The above applies to covalently bound atoms. We have still to deal with the partially ionic halogen atoms of the transition state. If they were fully ionic the appropriate radius would be the ionic radius, and it would be the same for all directions. We shall assume that, in the partially ionic halogens of transition states, the radius, at a given angular separation from the partially ionic bond, will be reduced below the ionic radius (which is practically the same as the maximal van der Waals radius) by half as much as, in a neutral atom, the

effective van der Waals radius, at the same angular separation from a full covalency, would be reduced below the maximal van der Waals radius :

$$\rho_{lon} - \rho_{\theta} = 0{\cdot}2(1 + \cos 2\theta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

with $\theta < 90°$. This formula is obviously consistent with our method of estimating the lengths of the carbon–halogen partial bonds in the transition states.

Table IV contains the angles which, in the models of the initial and transition states, the various " model distances " of Table III make with the directions of the covalencies or partial covalencies of the atom concerned. From these angles, and the values of $\rho_{max.}$ and ρ_{lon} in Table II, it is possible to calculate, using equations (1) and (2), the effective van der Waals distances, or " touching distances," corresponding to each of the tabulated model distances. By subtraction we can then find the " compression," experienced by the model of the initial or transition state as the case may be, in respect of each model distance which is shorter than the touching distance.

TABLE IV.

Angular Separations (θ) *in Degrees of Model Distances* (*Table III*) *from Covalency and Partial Covalency Directions.*

Key. (*a*) All alkyl groups with H_α atoms. (*b*) All alkyl groups with C_β atoms. (*c*) Ethyl, *iso*propyl, and *tert.*-butyl groups. (*d*) *n*-Propyl group. (*e*) *iso*Butyl group. (*f*) *neo*Pentyl group.

Bond or partial bond.	C_α–Br.	C_α–H_α.	C_α–C_β.	C_β–H_β.	C_β–C_γ.
Model dist.		*Initial state.*			
H_α . . . Br	24 (*a*)	46 (*a*)	—	—	—
C_β . . . Br	31 (*b*)	—	40 (*b*)	88 (*cde*)	149 (*d*), 88 (*ef*)
H_β . . . Br	46 (*cde*)	—	—	70 (*cde*)	—
C_γ . . . Br	20 (*d*), 53 (*ef*)	—	—	—	19 (*d*), 63 (*ef*)
H_γ . . . Br	17 (*d*), 65 (*ef*)	—	—	—	66 (*d*), 56 (*ef*)
		Transition state.			
H_α . . . Br	25 (*a*)	65 (*a*)	—	—	—
C_β . . . Br	34 (*b*)	—	56 (*b*)	60 (*cd*), 53 (*e*)	100 (*d*), 78 (*e*), 60 (*f*)
H_β . . . Br	54 (*cd*), 56 (*e*)	—	—	97 (*cd*), 105 (*e*)	—
C_γ . . . Br	48 (*d*), 57 (*e*), 64 (*f*)	—	—	—	54 (*d*), 71 (*e*), 86 (*f*)
H_γ . . . Br	67 (*d*), 73 (*e*), 81 (*f*)	—	—	—	67 (*d*), 77 (*e*), 90 (*f*)

The model distances, touching distances and compressions (in A.) for the various alkyl groups, in the initial and transition states of the bromine exchange reaction, are assembled in Table V, which also contains statements about the numbers of compressed distances affecting the energies of the states. We see at once that there is no compression worth mentioning in any initial state. Hence, although in principle the energy of steric hindrance must be calculated as a difference of compression energy in the initial and transition states, in practice

TABLE V.

Compressions in the Initial and Transition States of the Bromine Exchange Reaction.

	Model dists. (A.).	Touching dists. (A.).	Compressions (A.).	Number of compressed distances. Me.	Et.	Pr^β.	Bu^γ.	Pr^α.	Bu^{tw}.	*neo*Pentyl.
				Initial state.						
H_α . . . Br	2·50	2·44	None	[3	2	1	—	2	2	2]
C_β . . . Br	2·81	2·78	None	[—	1	2	3	1	1	1]
H_β . . . Br	2·98	2·86	None	[—	2	4	6	2	2	—]
C_γ . . . Br	4·22	2·49	None	[—	—	—	—	1	—	—]
	3·16	3·23	0·07	—	—	—	—	—	1	2
H_γ . . . Br	4·53	3·67	None	[—	—	—	—	2	—	—]
	3·05	3·07	0·02	—	—	—	—	—	2	4
				Transition state.						
H_α . . . Br	2·55	2·68	0·13	6	4	2	—	4	4	4
C_β . . . Br	2·78	3·01	0·23	—	2	4	6	2	—	2
	2·78	2·98	0·20	—	—	—	—	—	2	—
H_β . . . Br	2·43	3·01	0·58	—	2	4	6	2	—	—
	2·30	3·02	0·72	—	—	—	—	—	1	—
C_γ . . . Br	3·41	3·09	None	[—	—	—	—	2	—	—]
	2·88	3·34	0·48	—	—	—	—	—	2	—
	2·42	3·47	1·05	—	—	—	—	—	—	2
H_γ . . . Br	2·99	2·95	None	[—	—	—	—	2	—	—]
	2·71	3·05	0·34	—	—	—	—	—	4	—
	2·15	3·13	0·98	—	—	—	—	—	—	4

we may hereafter restrict attention to the transition state. We note the special position of the *neo*pentyl group, which alone involves compressions of the order of 1·0 A., whilst the other alkyl groups, except methyl, have compressions of the order of 0·6 A., and methyl scarcely any compression. It will be obvious from these figures alone that there is hope of providing a satisfactory explanation, on the basis of steric hindrance, of the peculiar facts about the *neo*pentyl halides to which Whitmore first called attention, and which are reduced to quantitative terms by the work of the preceding papers. The more does this seem likely when we remember the sudden way in which resistance to atomic compression mounts as the compression becomes greater.

We shall attempt to evaluate the significance of these compressions in terms of energy, but, before proceeding to further discussion of the bromine exchange reaction, we should point out that a qualitative similarity with reference to steric effects is to be expected of many of the commoner nucleophilic substitutions. This is because opposite, and therefore partly compensating, effects arise from changes in the size of the attacking and displaced groups. When the two bromine atoms of the above problem are replaced by two iodine atoms, the latter set themselves farther from C_α, and therefore farther from all the atoms of the alkyl group, in the transition state, so that all the model distances are increased; but, because of the larger ionic radius of iodine, so also are all the touching distances. The result is that the compressions are not greatly changed, as is shown in Table VI: even compressions of about 1·0 A. are only changed by 0·08 A. One can be sure without calculation that, if one of the two halogen atoms in the transition state were bromine and the other iodine, the compressions would lie between those appropriate to the symmetrical substitutions. Similar statements would be true if both or one of the bromine atoms of the original problem were chlorine, or if the bromide ion were a hydroxide ion.

TABLE VI.

Compressions in the Transition States of Halogen Exchange Reactions.

	Transition state compressions (A.).			Number of compressions.						
	Cl + RCl.	Br + RBr.	I + RI.	Me.	Et.	Pr$^\beta$.	Bu$^\gamma$.	Pr$^\alpha$.	Bu^{iso}.	*neo*Pentyl.
$H_\alpha \ldots Br$	0·10	0·13	0·16	6	4	2	—	4	4	4
$C_\beta \ldots Br$	0·18	0·22	0·27	—	2	4	6	2	2	2
$H_\beta \ldots Br$	0·52	0·58	0·64	—	2	4	6	2	—	—
	0·66	0·72	0·78	—	—	—	—	—	1	—
$C_\gamma \ldots Br$	0·39	0·48	0·55	—	—	—	—	—	2	—
	0·97	1·05	1·13	—	—	—	—	—	—	2
$H_\gamma \ldots Br$	0·25	0·34	0·44	—	—	—	—	—	4	—
	0·90	0·98	1·06	—	—	—	—	—	—	4

(b) *Dynamical Factors: Non-bonding Forces.*—We now continue the discussion of the bromine exchange reaction by calculating the energy values of the various compressions listed in Table V. We take account only of the compressions of transition states.

The energy ^pW of interaction of either of the bromine atoms of a transition state with any carbon or hydrogen atom, excepting C_α, is the sum of three contributions, of which the first two, ^pW_E and ^pW_D, are negative, and the third, ^pW_I, positive; the superscript p refers throughout to a particular pair of atoms:

$$^pW = {}^pW_E + {}^pW_D + {}^pW_I \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Here ^pW_E is the electrostatic energy, which we identify with its principal term, the induced dipole energy:

$$^pW_E = -\tfrac{1}{2}\alpha_1(e/2)^2/{}^pr^4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

This formula assumes that each bromine semi-ion of the transition state bears a charge $e/2$, where e is the electronic charge, $4{\cdot}80 \times 10^{-10}$ e.s.u. The charge creates a dipole of moment $\alpha_1(e/2)/{}^pr^2$ in the carbon or hydrogen atom; and the work of creating this dipole is ^pW_E. Since ^pr is taken as the internuclear distance, the assumption is implicit that both the charge and the dipole can be considered to be located at the centres of the respective atoms. The polarisability α_1 of the carbon or hydrogen atom is given by $3[R_1]/4\pi N$, where $[R_1]$ is the atomic refraction constant and N is Avogadro's number, $6{\cdot}024 \times 10^{23}$. We take $[R_1]$ for carbon as 2·41 c.c., and for hydrogen as 1·09 c.c. (Eisenlohr, "Spektrochemie," Enke, Stuttgart, 1912, p. 48). The accuracy of the calculation is not such as would justify a correction for dispersion. A reason is given later for the neglect of electrostatic energy terms dependent on more than two atoms.

The quantity ^pW_D is the so-called dispersion energy. We calculate it with the aid of London's formula,

$$^pW_D = -3\alpha_1\alpha_2 I_1 I_2/2(I_1 + I_2){}^pr^6 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where the subscripts 1 and 2 designate the atoms of the pair p, α_1, and α_2 are their polarisabilities, and I_1 and I_2 their ionisation potentials. Several of these quantities can be estimated only roughly. To obtain the polarisability α_2 of semi-ionic bromine, we estimate its refraction constant $[R_2]$ as 10·5 c.c., the mean between the constant, 8·8 c.c., of covalent bromine (Eisenlohr, *op. cit.*), and the constant, 12·2 c.c., of the dissociated bromide ion (Smyth, "Dielectric Constant and Molecular Structure," Chemical Catalog Co., 1931, p. 148). For the ionisation potentials of carbon and hydrogen atoms in alkyl groups we take 12·0 and 14·5 electron-volts respectively, these being Mulliken's estimates of the respective ionisation energies of a CC- and CH-electron in

ethane (*J. Chem. Physics*, 1935, **3**, 517). For the bromine ionisation potential we take the lower of Price's two values 10·5 and 10·8 electron-volts for methyl bromide, as deduced from the limits of Rydberg series in the vacuum ultra-violet (*ibid.*, 1936, **4**, 539). It is difficult to say how appropriate to our case this value may be; but a trial of various rough methods of allowing for the semi-ionic charge, and its solvation, suggests an uncertainty of the order of 10%, the effect of which is no greater than that of the other uncertainties of equation (5), and would make no important difference to our final results.

The term ^pW_I of equation (3) is much the most important, and represents the atomic interpenetration energy. Quantal calculations by Slater (*Physical Rev.*, 1928, **32**, 349) and others have indicated that the variation of ^pW_I with distance ^pr should be represented by an exponential law, $^pW_I \propto e^{^pr/a}$, rather than by any of the previously employed power laws. Born and Mayer have shown (*Z. Physik*, 1932, **75**, 1) that the exponential law gives a more satisfactory account, than do the power functions, of the properties of the alkali halide crystals. These authors empirically evaluated the length constant a, and found it to be substantially the same, 0·345A., for all alkali halides. On this evidence we use the equation

$$^pW_I = {}^pbe^{^pr/0\cdot345} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

in which ^pr is, of course, to be expressed in Ångström units. The important constant ^pb is evaluated from the consideration that the attractive and repulsive forces between the atoms balance at the touching distance:

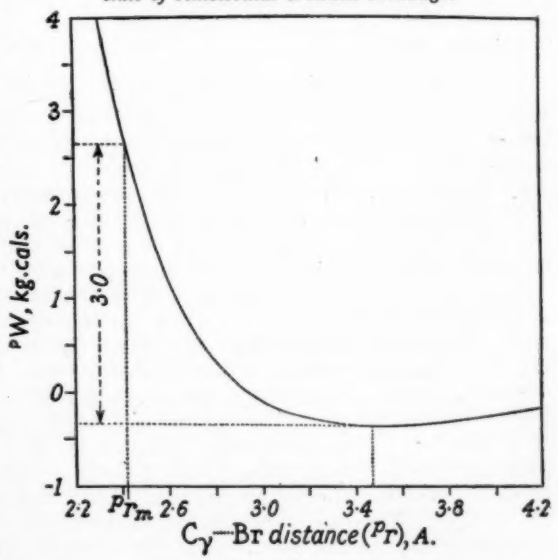
$$d^pW/d^pr = 0 \text{ when } {}^pr = {}^pr_t \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

It can now be explained why we neglect those terms of ^pW_E which depend in part on atoms outside the pair p, although the main such term, that dependent jointly on the two bromine atoms and the alkyl carbon atom, could easily have been taken into account. The reason is that the effect of this term on the touching distance is not allowed for, and therefore, since ^pb is estimated from the attractive forces which determine a particular touching distance, we should not include it amongst the forces used to determine ^pb. No such point arises with respect to ^pW_D, which is strictly additive in pairs of atoms.

As an illustration of the employment of equations (3)—(7) for the calculation of ^pW as a function of ^pr, Fig. 3 is given, which shows the results for the $C_\gamma \ldots$ Br distance in the transition state model for the bromine exchange reaction of *neo*pentyl bromide. It is observed that compression from the touching distance $^pr_t = 3{\cdot}47$ A. to the model distance $^pr_m = 2{\cdot}42$ A. involves an energy increase of 3·0 kg.-cals. per g.-mol. And, as Table V shows, there are two such compressed distances in the transition state. Similar calculations have been carried out, and curves drawn, for all the transition state compressions listed in Table V.

FIG. 3.

neo*Pentyl* $C_\gamma \ldots$ Br *compression energy in the transition state of bimolecular bromine exchange.*



It is necessary to consider the choice of the zero of non-bonding energy. As can be seen from Table V, all non-bonded distances in the initial state, corresponding to those which become compressed in the transition state, are quite close to the touching distances. This means that although the non-bonding forces are negligible in the initial state, the non-bonding energies of the various pairs of atoms are negative with respect to the conventional zero of energy corresponding to infinite atomic separation. These negative energies, " cohesion energies " as we may call them, are never more than 0·2 to 0·4 kg.-cal. for any particular pair of atoms, but the effect summed over all pairs is quite appreciable. Strictly, we should take account of the difference between this total cohesion energy of the initial and transition state, but, because, at this stage of our study of steric hindrance, we are adopting the simplification of omitting all calculations of non-bonding energy in the initial state, it is necessary to choose as appropriately as is possible in the circumstances our energy zero for calculations relative to the transition state. Our method is to regard compressions in the transition state as starting from the touching distances, rather than from infinite atomic separations. This amounts to supposing that the cohesion energies of the initial and transition states balance. The cancelling of the cohesion energies is, of course, an approximation, but it must be a considerably better approximation than taking account of cohesion energy in one state only. Therefore we transfer the energy zero as suggested, correcting the ^pW of equation (3) to $^pW'$, where

$$^pW' = {}^pW - {}^pW(^pr_t) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and $^pW(^pr_t)$ denotes the value of ^pW when $^pr = {}^pr_t$.

The energy $^pW'$ is a function of ^pr and can therefore be written $^pW'(^pr)$. Its value when ^pr is equal to the

model distance ${}^{p}r_m$ is denoted by ${}^{p}W'({}^{p}r_m)$. (This is the quantity which amounts to 3·0 kg.-cals. in the illustration of Fig. 3.) For each reacting system, we sum this quantity over all the transition state atom-pairs whose model distances are given in Table V.

$$W'_m = \sum_p {}^{p}W'({}^{p}r_m) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

The total, W'_m, represents a first upper limit to the increment of activation energy caused by steric hindrance: subject to the approximations made in the calculation, it is what the increment of activation energy would amount to if the bonding forces alone determined the geometry of the transition state, *i.e.*, if steric hindrance itself had no effect on the configuration of the state. The results of the summation are given in Table VII. The special position of the *neo*pentyl group is clearly in evidence. It will be noted that the methyl group can exert no steric effect on the bromine exchange reactions, and is therefore a possible reference group, by comparison with which the steric effects of other groups might be assessed from experimentally determined activation energies. It is also seen that the calculated upper limit to the increment of activation energy caused by the steric effect of the *neo*pentyl group in the bromine exchange reaction is about twice as great as the amount by which Table I indicates the activation energy of the substitution of *neo*pentyl bromide by ethoxide or iodide ions to exceed that of the corresponding substitution of methyl bromide.

TABLE VII.

First Upper Limits to Contributions of Steric Hindrance to the Activation Energies of Bromine Exchange, as Calculated by assuming Rigid Bonding Forces.

	Me.	Et.	Pr^{β}.	Bu^{γ}.	Pr^{α}.	Bu^{iso}.	*neo*Pentyl.
$H_\alpha \ldots Br$	0·0	0·0	0·0	—	0·0	0·0	0·0
$C_\beta \ldots Br$	—	0·2	0·4	0·5	0·2	0·2	0·2
$H_\beta \ldots Br$	—	0·7	1·5	2·2	0·7	0·6	—
$C_\gamma \ldots Br$	—	—	—	—	0·0	1·3	6·0
$H_\gamma \ldots Br$	—	—	—	—	0·0	0·2	6·4
W'_m (kg.-cals.)	0·0	0·9	1·9	2·7	0·9	2·3	12·6

(c) *Dynamical Factors: Bonding Forces.*—So far, our procedure has been to use the bonding forces in order to determine the geometry of the transition state, and then, assuming this geometry to persist in the presence of non-bonding forces, to calculate the non-bonding energy. This leads to an upper limit to the steric energy, as already described. The complete problem, however, needs a simultaneous evaluation of the geometry of the transition state and of its energy, the geometry being such as to minimise the total, bonding *plus* non-bonding, potential energy. Although we have not yet been able fully to solve this problem in a general form, the following considerations do lead to a solution when the model of the transition state possesses an axis of three-fold symmetry, and to closer upper limits to the steric energy in other cases.

As a simplification we concentrate attention on the weakest bonds in the transition state, the partly broken or partly formed covalencies by which the bromine atoms are bound, and assume that substantially the whole of the relief from non-bonding strain which the non-rigidity of the bonding forces can provide is furnished by the stretching and bending of these partial bonds. In other words, we assume that, in the presence of a steric effect, the only atoms which are seriously displaced from the positions we have hitherto assumed them to occupy are the bromine atoms. The number of possibly adjustable atomic co-ordinates is thus at once reduced to six. If we assume a plane of symmetry normal to the Br . . . Br line, the number of independent, possibly adjustable, parameters is then only three. Such a plane is present in all the transition states hitherto considered, except the one involving the *iso*butyl group. One parameter will measure the symmetrical stretching of the Br . . . C_α . . . Br system, and two others are available to define its bending. But the bending will take place in a plane, determined by the direction of the resultant pressure from the alkyl group, and if we choose one bending co-ordinate to be in this plane there will be no displacement in the other. Thus a large class of cases can be covered, in this approximation, if the total, bonding *plus* non-bonding, potential energy can be evaluated as a function of the two independent variables, x and y. We take the model positions of the two bromine atoms, 2·31 A. on each side of the α-carbon atom, as the origins of normal co-ordinates, and measure the outward displacements x of the bromine atoms along the axis containing the origins, and the lateral displacements y, parallel to each other and perpendicular to x, in the plane of the resultant displacements (Fig. 4). In those special cases in which the Br . . . Br line is a three-fold axis of symmetry there can be no displacement in the y direction, and hence the potential energy can be treated as a function of one variable only, namely x. Transition states involving the methyl and *tert.*-butyl groups belong to this specially simple class.

It is a simple matter to re-express the non-bonding energy as a function of x and y. Each ${}^{p}W'$ in equation (8) is a function of the appropriate ${}^{p}r$, the internuclear distance between the atoms concerned, one of which is always one of the bromine atoms. Once the plane of y is determined, by considerations either of symmetry or of dynamics, it is a purely geometrical problem to express ${}^{p}r$ in terms of x and y. By substitution, each term of the sum

$$W' = \sum_p {}^{p}W'(x, y) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

becomes a function of the same two variables, and W' can be plotted as an energy surface. For a reason which

will appear, we have had, for the purposes of this discussion, only to plot curves, of which Fig. 5 is a sample, showing W' as a function of x when $y = 0$—a section, that is to say, of the aforesaid surface. Such a curve has been plotted for each alkyl halide. The minimum value of W' is taken as the zero of energy.

The problem of expressing the bonding energy W'' of the Br . . . C_α . . . Br system as a function of its extension co-ordinate x and bending co-ordinate y has not yet been fully solved. By using partly empirical methods, an approach can be made towards the problem of estimating the dependence of W'' on x when $y = 0$. We carry the matter this far in the present paper, obtaining a definite estimate of the contribution of steric hindrance to the activation energy in those cases in which the symmetry of the system precludes bending of the Br . . . C_α . . . Br bond, and a second and closer upper limit to the steric contribution to the activation energy in other cases. The problem of calculating the bending potential energy function does not seem to be susceptible to a similarly simplified treatment, and we have as yet made no headway with the quantal calculations which appear to be the only alternative.

Let r_{00} be the equilibrium length of the C_α–Br bond in the initial state of the alkyl bromide, and r_0 the C_α–Br distance in the model of the transition state, assuming no deformation by non-bonding forces (r_{00} = 1·91 A. and r_0 = 2·31 A.). The general C_α–Br distance we shall take as $r = r_0 + x$, the system Br . . . C_α . . . Br being supposed linear. Following Ogg and Polanyi (*Trans. Faraday Soc.*, 1935, **31**, 604), we assume the activation energy of substitution to be the sum of five independent parts, r being so chosen that the sum shall

FIG. 4.

Transition state deformation co-ordinates in bromine exchange.

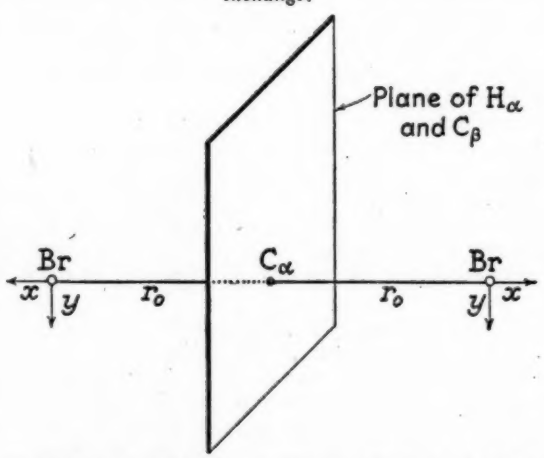
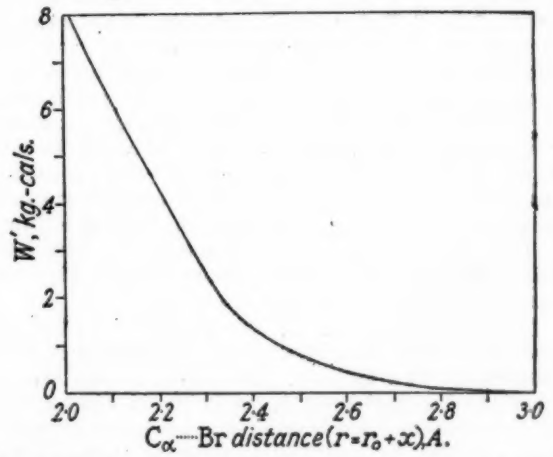


FIG. 5.

Total non-bonding energy as a function of C_α–Br *separation in the tert.*-Bu *transition state of bimolecular bromine exchange.*



be a minimum. The five contributions are: (*a*) the energy required to press the Br^- ion to a distance r from C_α; (*b*) the energy required to stretch the C–Br bond to a length r; (*c*) the work of replacing a solvent molecule by an alkyl halide molecule in the solvent shell of the bromide ion; (*d*) the work needed to bring into a plane three of the bonds of C_α; and (*e*) the electronic resonance energy. Ogg and Polanyi regard the resonance energy as small and neglect it. We doubt its smallness and have no need to neglect it; but we do neglect its variation with x over the small range of distances with which we are concerned.* We also treat the solvation and bond-bending contributions, (*c*) and (*d*), as independent of x. This leaves only the atom-pressing and bond-stretching contributions, (*a*) and (*b*), to be calculated as functions of x.

The calculation of the atom-pressing contribution (*a*) is treated as a two-atom problem, involving only the bromide ion and the α-carbon atom. All interactions involving the second bromine atom are neglected in this part of the calculation, since otherwise the energy could not be treated as independent of that of bond-extension, which is to be separately evaluated. Electrostatic interactions involving the two bromine atoms seem to be best classified along with the resonance energy, since the latter represents the electronic zero-point energy released when the anionic charge of the first bromine atom spills over into the second, and, if we were calculating it, we should have to assume an appropriate initial state of charge for the nominally neutral bromine atom. Any positive charge on the carbon atom is disregarded because the assumed van der Waals radius is that of the neutral atom, and the main point of calculating the attractive forces is to estimate resistance to compression from the fact that the attractive and compression forces balance at the van der Waals distance. We consider then, the action of a bromide ion on a neutral but polarisable carbon atom of van der Waals radius 1·6 A. (Table II), the valencies of which are supposed to have been displaced sufficiently not to affect approach of the bromide ion.

There will be three terms in this energy contribution. The first is the induced dipole energy which is to be calculated by means of an equation similar to (4), except that the factor $(e/2)^2$ must now be replaced by e^2.

* This may be justified because the resonance energy passes through its maximum in this region.

The second is the dispersion energy which is given by an equation similar to (5), in which α_2 and I_2 now refer to the polarisability and ionisation potential of a bromide ion. Its refraction constant $[R_2]$ we take as 12·2 c.c. (Smyth, *op. cit.*). The energy required to remove to infinity an electron from a solvated bromide ion is not known. The corresponding quantity is known for a gaseous bromide ion, and it has been calculated by Mott and Gurney for a bromide ion in a potassium bromide crystal (" Electronic Processes in Ionic Crystals," Oxford, 1940, p. 80). We take their figure, 9·0 electron-volts, as the better approximation, but realise that it may not be very accurate; fortunately it is not vitally important to have an accurate value. The third, and most important, part of the atom-pressing energy is the interpenetration energy, which is given by an equation similar to (6), in which the compression constant b has to be evaluated from the condition that the total of the three terms must pass through a minimum when $r = 1{\cdot}6 + 1{\cdot}95 = 3{\cdot}55$ A. Its value is $18{\cdot}5 \times 10^3$ kg.-cals., the complete equation for the energy of compression being

$$W_a'' = -158/r^4 - 810/r^6 + 18500 \text{ antilog}_{10}(-1{\cdot}259r) \quad . \quad . \quad . \quad . \quad . \quad (11)$$

Here W_a'' is in kg.-cals. if r is in Ångström units; and the zero of energy corresponds to infinite atomic separation.

The estimation of bond-stretching contribution (b) is likewise treated as a two-atom problem, to which, therefore, we can apply Morse's formula :

$$\left.\begin{aligned} W_b'' &= D\{e^{-2\alpha(r-r_{00})} - 2e^{-\alpha(r-r_{00})}\} \\ \alpha &= 0{\cdot}1227\omega\sqrt{\mu/D} \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Here W_b'' is given, relative to an energy zero at infinite atomic separation, in the same units as D, the dissociation of the C–Br bond reckoned from its potential energy minimum at $r = r_{00}$. The lengths r and r_{00} are in Ångström units, provided that the constant α is in reciprocal Ångströms; as in fact it is, if, in computing it by the formula given, both the vibration frequency ω and the dissociation energy D are expressed in terms of wave-numbers, and the reduced mass μ is expressed in ordinary atomic weight units.

Methyl bromide is a sufficiently good approximation to a diatomic molecule to be treated as a source of the parameters which are needed in order to apply the Morse equation to the C–Br bond of alkyl bromides. Owing to the lightness of the hydrogen atoms, and the slight coupling of their vibrations with those of the C–Br bond, the methyl group acts almost like a single atom of mass 15 with respect to the latter vibrations, of which the frequency ω is 594 cm.$^{-1}$ (Kohlrausch, " Smekal–Raman Effekt," Springer, 1931, p. 307), and the mass factor μ is 12·6 atomic weight units. We take the dissociation energy D as 70·6 kg.-cals. = $70{\cdot}6 \times 351{\cdot}6$ cm.$^{-1}$, this being Baughan and Polanyi's value (*Nature*, 1940, **146**, 685), corrected for the zero-point energy of the C–Br vibrations. These data give $\alpha = 1{\cdot}64$ A.$^{-1}$.

By adding W_a'' and W_b'' we obtain W''_{a+b}, a function of r which passes through a minimum value, − 43·2 kg.-cals., when $r = 2{\cdot}25$ A. This minimum lies above the energy minimum of the Morse curve of methyl bromide by 27·4 kg.-cals. The defect of this energy below the activation energy of the bromine exchange reaction of methyl bromide, probably 18—19 kg.-cals., may be taken to represent the total (negative) value of the solvation, bond-bending and resonance contributions, (*c*), (*d*), and (*e*), to the activation energy; for there is no non-bonding contribution to the activation energy of this reaction (*p.* 182). The fact that the mimimum occurs at $r = 2{\cdot}25$ A., and not, as exact consistency would demand, at $r = r_0 = 2{\cdot}31$ A., may be a result of the approximations we have made, particularly, perhaps, the assumption that the three contributions (*c*), (*d*), and (*e*) to the activation energy can be treated as independent of r; alternatively, our original estimate of 2·31 A. may be slightly too high, though a closer agreement could hardly have been expected.* In order to bring our calculation of the dependence upon $r = r_0 + x$ of the bonding energy of the transition state into a form in which, by combination with our previous estimates of the non-bonding energy, we can find out how much of the latter is released, and how much becomes converted into bonding energy, through the stretching of the Br . . . C_a . . . Br system, we draw new axes to the curve of W''_{a+b} so that its minimum rests upon an energy origin at $x = 0$:

$$W''(x) = W_a''(r - 0{\cdot}06) + W_b''(r - 0{\cdot}06) + 43{\cdot}2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

where $x = r - 2{\cdot}31$ A. In short, we treat the small discrepancy of 0·06 A. as affecting the position of the curve, but not its shape.

The lowest curve of Fig. 6 is the curve of this equation. It represents a section, cut at 45° through the origin, of the conventional energy surface, in rectangular co-ordinates, for the linear three-particle reaction, and viewed as a projection on one of the co-ordinate planes, *i.e.*, reduced in one direction by the factor $1/\sqrt{2}$. It is assumed to apply to all the alkyl bromides. In order to take account of the non-bonding energy we utilise the curves of equation (10) with $y = 0$, curves of the type of which Fig. 5 is an example : there is one such curve for each alkyl halide. By adding the ordinates of each of these W' curves to those of the common W'' curve, we obtain $W = W' + W''$ curves, one for each alkyl halide, which all show minima variously shifted towards positive values of x, and variously raised with respect to energy. Sample W curves are shown in Fig. 6, including one for the bromine exchange reaction of *tert.*-butyl bromide and one for that of *neo*pentyl bromide.

The energies at the minima represent the various steric effects, as far as we have calculated them, on the activ-

* It is doubtful whether any of the distances given in this paper (except covalent radii) are reliable to within 0·05 A.

ation energy of the substitution. They should be equal to the steric contribution to the activation energy in the cases of methyl and *tert.*-butyl bromides, but only an upper limit in other cases in which bending of the Br . . . C_α . . . Br system, which we have had to neglect, can release part, as well as storing part, of the calculated potential energy. The values obtained are in Table VIII. Fig. 6 again emphasises the special position of the *neo*pentyl group as a source of steric hindrance, since the curves for all the other alkyl groups treated fall between the curves shown for the methyl and the *tert.*-butyl group.

TABLE VIII.

Calculated Values of, or Limits to, the Steric Activation Energy of Bromine Exchange (Linear Transition State).

	Me.	Et.	Pr^β.	Bu^γ.
W_m (rigid model—Table VII)	0·0 kg.-cals.	0·9 kg.-cals.	1·9 kg.-cals.	2·7 kg.-cals.
$W_{min.}$ (with $BrC_\alpha Br$-stretching)	0·0 kg.-cals.	0·7 kg.-cals.*	1·4 kg.-cals.*	2·2 kg.-cals.
$2x_{min.}$ (amount of stretching)	0·00 A.	0·02 A.	0·04 A.	0·07 A.
	Pr^α.	Bu^{iso}.	*neo*Pentyl.	
W_m (rigid model—Table VII)	0·9 kg.-cals.	2·3 kg.-cals.	12·6 kg.-cals.	
$W_{min.}$ (with $BrC_\alpha Br$-stretching)	0·7 kg.-cals.*	—	11·7 kg.-cals.*	
$2x_{min.}$ (amount of stretching)	0·02 A.	—	0·11 A.	

* Upper limits.

(d) *Comparison with Experiment.*—For the representation of experimental data we use the Arrhenius equation, $k_2 = Be^{-E/RT}$ and not any of the modified forms which have been proposed, since it is generally recognised that no simple and universal temperature function is adequate to express the temperature dependence of the Arrhenius parameters. It will therefore be understood that the Arrhenius activation energy should never be exactly equal to the theoretically calculated activation energy, though we have no easy way of estimating the difference, which is presumed to be small.

The simplest comparisons are with the β-methylated alkyl groups, since β-branches in the alkyl group are unlikely to contribute any notable polar effect to the energy of activation (because of the loss which polar effects suffer on transmission through saturated carbon chains). As we have concluded before, and shall confirm in the course of the present discussion, α-branches in alkyl groups give rise to a very appreciable polar effect in bimolecular reactions.

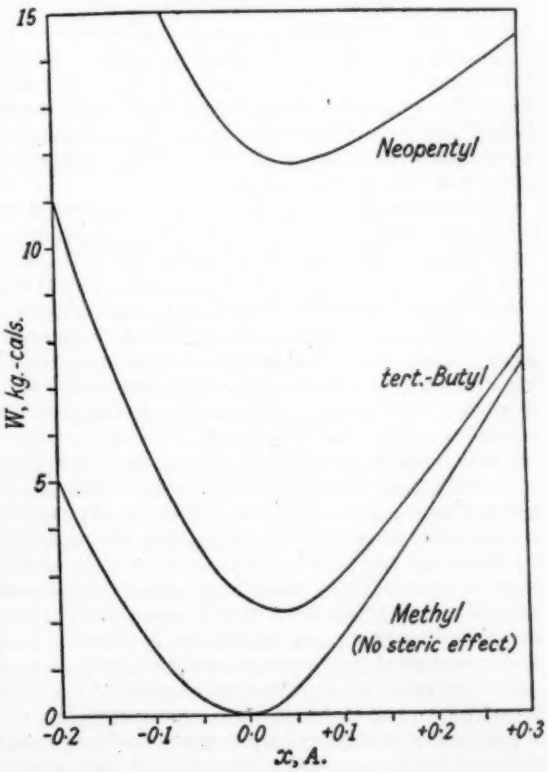
Using radio-bromine as an indicator of exchange, le Roux and Sugden (J., 1939, 1279) and Elliot and Sugden (J., 1939, 1836) have measured the rates of the bromine exchange reaction of three primary alkyl bromides in "90%" acetone at several temperatures.* From the graphs of their values for $\log_{10} k_2$ against $1/T$, we obtain the following Arrhenius activation energies (in kg.-cals.): † *n*-Propyl, ~19; *n*-Butyl, 19·3; *iso*Butyl, 20·6.

So far as the steric effect is concerned the exchange reactions of ethyl, *n*-propyl, and *n*-butyl bromides should have the same activation energy, whilst the reaction of *iso*butyl bromide should have an activation energy about 1·4 kg.-cals. greater (certainly less than 2·3 kg.-cals. greater). The observed difference of 1·3 kg.-cals. between the values for *n*- and *iso*-butyl bromides agrees satisfactorily with these theoretical estimates.

A comparison between ethyl and *iso*butyl bromides with respect to substitution by ethoxide ions in ethyl alcohol is available in Table I (p. 175): the Arrhenius activation energy for the ethoxylation of *iso*butyl bromide is 1·8 kg.-cals. greater than for the corresponding reaction of ethyl bromide. It is true that we have not carried out a calculation for the ethoxylation process; but it has been pointed out (p. 180) that theory indicates the steric effect on activation energy to be not very

FIG. 6.

Total potential energy as function of C_α–Br *separation in linear transition states of* Br *exchange with and without steric hindrance.*



* They calculated activation energies from a modified Arrhenius equation (containing a $\sqrt{T}$ factor), and their values are therefore slightly different from those now quoted.

† The slope of the graph for *n*-propyl bromide is not very exactly defined by the experimental points, and hence the Arrhenius energy is given only in an approximate form.

sensitive to the size of the ionic reagent; and, on the experimental side, Table I itself shows, particularly in relation to the reactions of *neo*pentyl bromide, that quite similar steric effects on activation energy arise in ethoxylation and in halogen exchange. Thus the observed difference of activation energy for the ethoxylation of ethyl and *iso*butyl bromide is roughly of the expected magnitude.

The outstanding steric effect revealed in Table I is that shown by *neo*pentyl bromide in both halogen exchange and ethoxylation, and represented in either case by about 6 kg.-cals. of activation energy. Our calculated upper limit of 12 kg.-cals. to the steric increment of activation energy is expected to be considerably above the true increment, because so great a strain in the transition state will undoubtedly be largely relieved by the bending of the $BrC_{\alpha}Br$ system, the effect of which we have not calculated. As Table VII shows, the stretching of the $BrC_{\alpha}Br$ system releases about 1 kg.-cal. from the potential energy of the transition state. Since, with full covalencies, the forces which resist bending are always several times weaker than those which oppose stretching, it is a reasonable expectation that the bending of the $BrC_{\alpha}Br$ system will release several more kg.-cals. Thus our calculated upper limit of 11·7 kg.-cals. is not irreconcilable with the observed value of 6 kg.-cals. in the substitutions studied.

We now turn to the α-methylated alkyl groups: here, if anywhere, a polar effect, as well as a steric effect, is to be expected. Using radio-iodine as an isotopic indicator, McKay has measured the rate of exchange between iodide ions and various primary and secondary alkyl iodides in alcohol at various temperatures (*J. Amer. Chem. Soc.*, 1943, **65**, 702). He reports definite differences in the Arrhenius activation energies for the primary and secondary iodides: for ethyl iodide and its primary homologues the values were grouped around 19·0 kg.-cals., whilst *iso*propyl and *sec.*-butyl iodides gave about 20·5 kg.-cals. Professor Sugden has kindly shown us the manuscript of a forthcoming paper by le Roux, Lu, Sugden, and Thomson.* Using radio-active bromine as an indicator for exchange, these authors have measured the rates of the bromine exchange reaction of a primary, a secondary, and a tertiary alkyl bromide, at a number of temperatures in ethylene diacetate as solvent. By plotting their values of $\log_{10} k_2$ against $1/T$, we obtain the following Arrhenius activation energies (kg.-cals.): † *n*-Butyl, 18·2; *iso*Propyl, 20·0; *tert.*-Butyl, ~23.

The activation energy of the reaction of methyl bromide is unknown, but we may assume that the observed value for *n*-butyl bromide would approximately apply to ethyl bromide. Taking this as the starting point, the increase of activation energy is found to be 1·8 kg.-cals. in the reaction of *iso*propyl bromide, and about 5 kg.-cals. in that of *tert.*-butyl bromide. As Table VII shows, theory indicates that the steric increase of activation energy should be about 0·7 kg.-cal. (certainly not more than 1·4 kg.-cals.) for *iso*propyl bromide, and about 2 kg.-cals. (not more than 2·2 kg.-cals.) for *tert.*-butyl bromide. The observed increases are considerably larger, and we attribute the amounts by which they exceed the calculated values to the expected polar effects of the additional α-methyl substituents in the secondary and tertiary alkyl groups (Hughes and Ingold, J., 1935, 244; cf. this paper, p. 174).

The relatively small steric effect calculated for bimolecular halogen exchange in *tert.*-butyl compounds, contrasted with the large steric effect calculated for, and found in, *neo*pentyl compounds, illustrates the difference between the classical picture of steric hindrance and the new treatment of this phenomenon. We think that no one acquainted with Victor Meyer's experiments, showing how steric hindrance in the esterification of *o*-disubstituted benzoic acids largely disappeared when an interposed methylene group removed the carboxyl group one atom further away from the branched structure, as in correspondingly substituted phenylacetic acids, would have predicted, before the immediate foundations of the present work were laid, that steric effects which were relatively weak in the bimolecular substitutions of *tert.*-butyl halides would be strongly *enhanced* when an interposed methylene group removes the displaced halogen one atom further from the branched structure, as in *neo*pentyl halides.

It remains to be pointed out that steric hindrance must affect not only the energy, but also the entropy, of activation, *i.e.*, the probability factor of reaction rate. It is easily seen how a development of the considerations which have been outlined could lead to an evaluation of the steric effect on the entropy of activation. It is essentially a question of calculating the partition function of the transition state, or at least those factors of the partition function which do not approximately cancel similar factors in the partition function of the initial state in the complete statistical mechanical expression for reaction rate. As data we require the dimensions and vibration frequencies of the transition state. Part of such a calculation could be carried through now, using the positions and curvatures (leading to frequencies) of W–x curves, such as are illustrated in Fig. 6; but even for trigonally symmetrical transition states, such as the *tert.*-butyl group would yield, the calculation could not now be completed, because we do not yet know the $BrC_{\alpha}Br$ bending potential energy function, and therefore cannot estimate the bending frequency, which, because of its lowness, is likely to be an important determinant of the entropy. We are trying suitably to extend and improve the calculations, concurrently with the development of more accurate and crucial experimental tests.

(B) *Further Review of Bimolecular and Unimolecular Nucleophilic Substitutions in Relation to Steric Effects.*

(a) *Steric Hindrance in Bimolecular Nucleophilic Substitution.*—1. *Reactions of halogen compounds.* Many years ago one of us made attempts to open a route to the preparation of *spiro*-compounds by condensation of

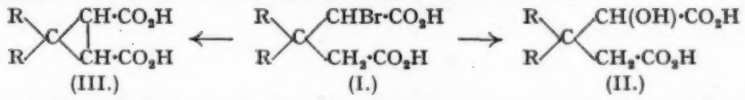
* This paper has since appeared (J., 1945, 586).

† The slope of the graph for *tert.*-butyl bromide is not very exactly defined by the experimental points, and therefore the Arrhenius activation energy is given only in an approximate form.

pentaerythrityl tetrabromide, $C(CH_2Br)_4$, with such compounds as potassium cyanide, ethyl sodiomalonate, ethyl sodiocyanoacetate and ethyl disodioethanetetracarboxylate. These attempts, which have remained unrecorded, were frustrated by the marked lack of reactivity of the bromide. It was only afterwards learnt by private discussion that the late W. H. Perkin, junr., at a still earlier period, had made some similar experiments, with a like result. According to the organic chemical ideas of those days, the concept of steric hindrance could not be very plausibly associated with the halogen reactions of a compound the bromine atoms of which all project outwards from the corners of a regular tetrahedron. We now realise, however, that pentaerythrityl tetrabromide is a substituted *neo*pentyl bromide, and that accordingly its bimolecular substitutions are of necessity sterically hindered. The example illustrates very well the difference in point of view which results from the association of the older notions of steric hindrance with our modern ideas on reaction mechanism.

A similar example exists, which has before received some public notice: trimethylene dibromide, $BrCH_2{\cdot}CH_2{\cdot}CH_2Br$, has a normal reactivity towards nucleophilic reagents, but ββ-dimethyltrimethylene dibromide, $BrCH_2{\cdot}CMe_2{\cdot}CH_2Br$, is said to be extremely inert (Hickinbottom, " Reactions of Organic Compounds," Longmans, 1936, p. 365). The explanation is clearly the same.

With this case as a connecting link, we may reconsider some of the experimental evidence which has been interpreted by means of the valency deflexion hypothesis of Thorpe and Ingold; for it seems certain now that at least some of the observations which this hypothesis was employed to correlate are susceptible of explanation on more general lines. A typical example is provided by the alkaline hydrolysis of various α-bromoglutaric acids, including the acid not otherwise substituted, β-alkylated acids, ββ-dialkylated acids, and acids with the β-carbon atom forming part of an alicyclic ring. These acids (I) when hydrolysed with alkalis yield two main products, *viz.*, the α-hydroxyglutaric acid (II) (which is always isolated as its γ-lactonic acid), and the *cyclo*propane-1 : 2-dicarboxylic acid (III). The special point, which the valency deflexion hypothesis was brought in to explain, was that, as the β-hydrogen atoms of the parent compound were successively replaced by alkyl groups, the proportions in which these two products were formed under fixed conditions progressively shifted in the direction favouring the ring-compound (Ingold, J., 1921, **119**, 305; 1922, **121**, 2676; cf. Beesley, Ingold, and Thorpe, J., 1915, **107**, 1080; and Baker and Ingold, J., 1923, **123**, 122):



(III.) (I.) (II.)

When dilute aqueous sodium carbonate was the reagent, the hydroxy-acid (II) was the main product in all cases; but when concentrated potassium hydroxide was employed, more and more of the hydroxy-acid, the quantity depending on the number, and to some extent the size, of the β-alkyl groups, became replaced in the product by the ring compound (III).

Our present interpretation of these facts would be on the following lines. In all cases, and under all conditions, the compound hydrolysed is not the bromo-acid, but is its anion, $\bar{C}O_2{\cdot}CH_2{\cdot}CR_2{\cdot}CHBr{\cdot}\bar{C}O_2$, or possibly, in some circumstances, the acid anion $CO_2H{\cdot}CH_2{\cdot}CR_2{\cdot}CHBr{\cdot}\bar{C}O_2$. The electron repulsion of a $\bar{C}O_2$ group adjacent to a bromine-bearing carbon atom produces, as we already know, a definite tendency to unimolecular substitution, S_N1, a reaction mechanism which, as will be emphasized later, is not subject to steric hindrance. In particular we can be sure, by reference to existing experimental data, that, with aqueous sodium carbonate as the reagent, the principal hydrolytic mechanism would be the unimolecular one (Cowdrey, Hughes, and Ingold, J., 1937, 1217; *idem* and Masterman and Scott, J. 1937, 1254). When this reagent is replaced by concentrated potassium hydroxide, the unimolecular mechanism must become replaced by the bimolecular mechanism of substitution, S_N2; or, in a case in which a bimolecular elimination, $E2$, is also possible, the unimolecular solvolysis, S_N1, will become replaced by a total bimolecular reaction, substitution plus elimination, $S_N2 + E2$, which will grow in importance with the increasing concentration of hydroxide ions. In the anion of the parent α-bromoglutaric acid, the substitution part of this total bimolecular reaction, S_N2, is not sterically hindered to any serious extent. However, the anion of α-bromo-β-methylglutaric acid is a substituted *iso*butyl bromide; and the anion of α-bromo-ββ-dimethylglutaric acid is a substituted *neo*pentyl bromide. Thus the bimolecular substitution, which can take place freely in the unalkylated substance, is more or less markedly impeded in the β-methyl derivative, and practically stopped altogether in the ββ-dimethyl compound. In the meantime there is nothing to prevent the concomitant bimolecular 1 : 3-elimination process, $E2$, which will not be sterically hindered to anything like the same extent, because it depends on attack by the hydroxide ions on the potentially ionisable α′-hydrogen atom (rather than on the less accessible α-carbon atom), from making the best of the situation created by the difficulties which face its competitor. Of course, a kinetic investigation is necessary to prove this theory, but its internal consistency seems to be a strong point in its favour.

Since the essence of the valency deflexion hypothesis is that the angular parameters of a molecular structure, as it would have been determined by the bonding forces, become modified by the non-bonding repulsive forces, the old theory (like the classical theory of steric hindrance) may be regarded as absorbed in the new. However, the differences should not be minimised: the concentration of attention in the new theory on the transition state seems particularly important for the development of spatial explanations having such quantitative objectives as would have been considered inappropriate to organic chemists in an earlier epoch.

McDonald, Rothstein, and Robison recently reported (*J. Amer. Chem. Soc.*, **1944**, **66**, 1984) that *iso*butyl chloride is much less reactive than *iso*amyl chloride towards potassium iodide in acetone. They expressed surprise at the observation, which, since the reaction in this solvent is always bimolecular, is fully consistent with our observations and calculations (pp. 175 and 180).

2. *Reactions of alcohols.* The sharper definition of our views on steric hindrance permits further consideration of the group of reactions by which alcohols may be converted into alkyl halides by means of thionyl chloride, phosphorus halides and hydrogen halides. These reactions were discussed by Cowdrey, Hughes, Ingold, Masterman, and Scott (*loc. cit.*), but almost entirely on the basis of data relating to optical activity, no kinetic evidence being then available. It was supposed that the first stage was always the formation of a complex, such as Alk·O·SOCl or Alk·OH·H·Br; which might then rearrange with retention of configuration in the alkyl group, (S_Ni), provided there was a sufficient electron supply in the alkyl group to permit the breaking of the C–O bond; alternatively, the complex could ionise one halogen atom. If, in the latter case, on account of the positive charge produced in the residual cation, the electron supply in the alkyl group became sufficient, the C–O bond might break at this stage, producing a carbonium ion, and a largely racemised substitution product (S_N1). If, on the other hand, the electron supply remained insufficient, a bimolecular attack by the halide ion on the α-carbon atom of the alkyl group would supervene, and the produced alkyl halide would have an inverted configuration (S_N2). These ideas may be illustrated thus:

$$R_1R_2R_3C\cdot OH \longrightarrow R_1R_2R_3C\overset{O}{\underset{Cl}{}}SO \longrightarrow R_1R_2R_3CCl + SO_2 \quad (S_Ni)$$

$$R_1R_2R_3\overset{+}{C}{-}O\overset{+}{S}O + \bar{C}l \longrightarrow Cl\cdot CR_1R_2R_3 + SO_2 \quad (S_N2)$$

$$R_1R_2R_3\overset{+}{C} + SO_2 + \bar{C}l \longrightarrow R_1R_2R_3CCl + SO_2 \quad (S_N1)$$

The tendency to mechanism S_Ni was most marked with thionyl chloride, though, even with this reagent, it was suppressed in conditions conducive to the ionisation of the halogen atom. With hydrogen halides, to go to the other extreme, mechanism S_Ni was very difficultly available, since the ionisation of the halogen atom could scarcely be stopped. So far as the evidence of optical activity disclosed the situation, mechanisms S_Ni and S_N1 required the presence of an electron-releasing α-aryl group in the alkyl group: secondary alcohols used mechanism S_N2, except when such an unsaturated group was attached to the α-carbon atom. Presumably, therefore, aliphatic primary alcohols would be entirely restricted to the use of mechanism S_N2. There was no direct evidence from optical activity relating to tertiary alcohols, but, by analogy with the behaviour of halides and ammonium and sulphonium ions, we should expect that, when an α-arylated secondary alkyl compound can split up to give a carbonium ion, an analogous tertiary alphyl compound should also be able to do so.*

We now have a supplementary criterion of mechanism, since the bimolecular process, S_N2, must be subject to drastic steric hindrance in structures of the *neo*pentyl type, whilst the alternative mechanisms, S_Ni and S_N1, will not be sterically hindered to any comparable extent. However, as noted, mechanisms S_Ni and S_N1 should be unavailable, or at most difficultly available, to saturated, primary aliphatic alcohols, though either might become readily available in secondary alcohols with an α-aryl substituent, or in tertiary alcohols. It is consistent that *neo*pentyl halides cannot be prepared by the action of thionyl chloride, or the halides of phosphorus or of hydrogen, on *neo*pentyl alcohol (Whitmore and Rothrock, *J. Amer. Chem. Soc.*, **1932**, **54**, 3431). Contrary to statements by Tissier (*Ann. Chim. Phys.*, **1893**, **29**, 34) and Richard (*ibid.*, **1910**, **29**, 344), no *neo*pentyl chloride could be obtained by Whitmore by the use of hydrogen chloride, whilst prolonged treatment of *neo*pentyl alcohol with hydrogen bromide gave a mixture of bromides formed largely through rearrangement of the carbon structure. The general result confirms the conclusion that a bimolecular mechanism, S_N2, is normally the only one available to saturated primary alcohols; whilst it will be clear from Part XXIX (this vol., p. 166; cf. also p. 192) that the observation of rearrangement on prolonged treatment with hydrogen bromide means that the mechanism next in order of availability, when the bimolecular mechanism is ruled out by steric hindrance, is, as we should have expected for hydrogen halide reactions, the unimolecular mechanism S_N1, dependent on the intermediate formation of a carbonium ion. Consistent again is the observation of Bartlett and Knox (*J. Amer. Chem. Soc.*, **1939**, **61**, 3184) that αα-diethyl*neo*pentyl alcohol is converted into the chloride "instantly" by dry hydrogen chloride. In this alcohol the steric inhibition of the bimolecular mechanism must be even stronger than in *neo*pentyl alcohol. But diethyl*neo*pentyl alcohol is a tertiary alcohol, and therefore readily yields the carbonium ion, which is the essential intermediate in the unimolecular mechanism. Thus the new criterion provides good confirmation of two of the mechanisms postulated in **1937** for this group of reactions. A survey, from our present point of view, of the work of Bennett and Reynolds (J., 1935, 131) on the rate of reaction of hydrogen bromide with alcohols in phenol as solvent, concerning which no certain conclusion could be reached in **1937** (Cowdrey *et al.*, *loc. cit.*, p. 1269), strongly suggests that the bimolecular mechanism was under observation, as is indicated particularly by the low reaction rates observed for *iso*butyl alcohol.

3. *Reactions of carboxyl compounds.* Probably no subject has been more discussed in relation to steric

* The reactions of α-phenylethyl and *tert.*-butyl halides, etc., are very similar with regard to mechanism.

hindrance than carboxyl esterification and hydrolysis. We know now that the subject is more complicated than used to be thought, inasmuch as seven mechanisms have been recognised (Datta, Day, and Ingold, J., 1939, 838; Hughes, Ingold, and Masterman, *ibid.*, p. 840), four of which are bimolecular and should therefore be subject to steric hindrance (Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686). Two of them, the commonly observed acid- and base-catalysed reactions involving acyl–oxygen fission, R–CO|OR′, are well known to be. One of the three unimolecular mechanisms, the acid reaction with acyl–oxygen fission, is known not to be (see below). The evidence is summarised by Day and Ingold (*loc. cit.*). The other mechanisms await the completion of kinetic investigations now in progress.

Concerning bimolecular reactions with acyl–oxygen fission, the reason why *neo*pentyl alcohol esterifies at a normal rate with carboxylic acids, in contrast to its behaviour towards halogen acids (Quayle and Norton, *J. Amer. Chem. Soc.*, 1940, **62**, 1170), is that the mode of fission *is* acyl–oxygen: as compared to the reaction with halogen acids, there is one more atom between the seat of attack of the nucleophilic reagent and the groups which, in the formation and hydrolysis of halides, are mainly responsible for the steric hindrance. The nearest analogies, amongst carboxyl reactions with acyl–oxygen fission, to the conditions of steric hindrance present in the bimolecular nucleophilic substitutions which might form or destroy *neo*pentyl halides, would arise in the hydrolysis of *tert.*-butyl esters, or, alternatively, esters of trimethylacetic acid, or, of course, in the formation of such esters by direct esterification. In fact, these reactions are known to be slow * (cf. data by Skrabal, Sudborough, and others, summarised by Hammett, "Physical Organic Chemistry," McGraw-Hill, 1940, pp. 211—213; also Evans, Gordon, and Watson, J., 1938, 1439). They are not extremely slow like the substitution of *neo*pentyl halides, but then the steric hindrance is not expected to be so marked, since the unsaturation of the carboxyl group allows a transition state with only four groups attached to the seat of substitution. In some experiments which are not yet complete enough for publication it has been found that the rates of bimolecular substitution of tritylmethyl chloride, $Ph_3C{\cdot}CH_2Cl$, are extremely low, an effect obviously attributable to steric hindrance. Consistently, triphenylacetic acid, $Ph_3C{\cdot}CO{\cdot}OH$, has recently been shown to be notably inert in esterification (Smith and Burn, *J. Amer. Chem. Soc.*, 1944, **66**, 1494). We are using this method of stopping nucleophilic attack on the carboxyl carbon atom (and therefore stopping acyl–oxygen fission) in a concurrent investigation of the kinetics and stereochemical course of carboxyl esterification and hydrolysis with alkyl–oxygen fission, R·CO·O|R′.

(b) *Superposed Polar and Steric Effects in Bimolecular Nucleophilic Substitution.*—The problems of evaluating these effects in superposition could, of course, be more advantageously discussed if we had more strictly quantitative information about the steric effect; but it seems desirable, even at this stage, to review the position with respect to the series of α-methylated alkyl groups, the study of which played a large part in the original recognition of the bimolecular and unimolecular mechanisms of substitution. It was noted then (1933; 1935) that rates of bimolecular substitutions, particularly of the hydrolytic and alcoholytic substitutions of halides, descended in the series CH_3, $MeCH_2$, Me_2CH (not much was known about bimolecular substitutions with the group Me_3C). It was suggested that the polar effects of the alkyl groups might account for the observed trend, the conclusion being subject to possible quantitative modification on account of steric effects (Hughes and Ingold, J., 1935, 244).

We can assume as a first approximation that, compared to the polar effects of the successively introduced methyl groups in the α-methylated series, CH_3, $MeCH_2$, Me_2CH, Me_3C, the polar effects of the methyl groups of the β-methylated series, $CH_3{\cdot}CH_2$, $MeCH_2{\cdot}CH_2$, $Me_2CH{\cdot}CH_2$, $Me_3C{\cdot}CH_2$, are negligible. This is because of the large loss by relay through a saturated carbon atom which is a recognised characteristic of the inductive effect. Accordingly, our observations of the rate changes in the β-methylated series will represent a practically pure steric effect. And the trends have been accounted for by calculation, not very precisely, but consistently enough to suggest that limited conclusions could be drawn by application of the same methods of calculation to the α-methylated series, where a real problem of the superposition of effects arises. Such calculations make it seem unlikely that the factor of 18, by which at 55° the rate of alkaline alcoholysis decreases from methyl bromide to ethyl bromide (Table I, p. 175), is wholly to be explained as a steric effect. The calculated upper limit to the steric increment of activation energy for bromine exchange is 0·7 kg.-cal. (Table VIII, p. 185), an energy difference corresponding to a rate-ratio of about 3. Much the same can be said of the factor of 34, which represents the observed further decrease of rate on passing from ethyl bromide to *iso*propyl bromide (Bateman, Cooper, Hughes, and Ingold, J., 1940, 925). The calculated steric effect would be of the same order of magnitude as in the previous comparison. Thus the question which we had to leave open in 1935 as to how much, if any, of the rate decrease in the α-methylated series was to be attributed to the steric factor seems now to be tentatively answerable in the statement that a substantial part, though not the whole, of the observed effect is of steric origin (cf. Evans and Polanyi, *Nature*, 1942, **149**, 608).†

Confirmation of this conclusion follows from the already mentioned measurements, recently made by

* The record for one of three reactions, the acid-catalysed hydrolysis of *tert.*-butyl acetate (Hammett, *op. cit.*) does not indicate a slow reaction: but this may well be due to the incursion of alkyl–oxygen fission, R·CO·O·|R′, in view of Cohen and Schneider's demonstration that this type of reaction does in fact occur in the analogous case of *tert.*-butyl benzoate (*J. Amer. Chem. Soc.*, 1941, **63**, 3382).

† It must be remembered that near the mechanistic transition point a reaction may pursue a marginal mechanism, which, though kinetically of the second order, may exhibit in an incipient form some of the characteristics of the unimolecular process, notably in relation to the dependence of rate on structure (Hughes, Ingold, and Shapiro, J., 1936, 225).

Sugden and his collaborators with the aid of radio-bromine, of the activation energies of the bromine exchange reactions of typical primary, secondary and tertiary alkyl bromides (cf. p. 186). The observed primary–tertiary difference of activation energy is 5 kg.-cals., considerably greater therefore than 2 kg.-cals., the estimated difference due to steric causes only. The balance may be interpreted as a polar effect of the additional α-methyl substituents in the tertiary alkyl group; and it appears that the polar and steric effects of the α-methyl substituents of alkyl groups may be of comparable importance in bimolecular nucleophilic substitutions. A similar conclusion follows if we consider the primary–secondary, or secondary–tertiary difference of activation energy.

When we compare the observed increments of activation energy in the β-methylated alkyl series with the estimated steric contributions, no similarly obvious margin of energy appears which could be attributed to polar effects (cf. p. 185). In this series polar effects seem to be of an altogether smaller order of magnitude, as we should have expected from the elementary theory of the general inductive effect.

(c) *Steric Hindrance and the Unimolecular Mechanism of Nucleophilic Substitution.*—1. *Reactions of halogen compounds.* We now take a comparative view of the rate data contained in four of the preceding papers (Parts XXVI, XXVIII, XXX, and XXXI). Some of the more significant figures are collected in the form of relative rates in Table IX ($CH_3{\cdot}CH_2{\cdot} = 1$ or $CH_3{\cdot}CMe_2 = 1$). Those cases in which the mechanism of substitution is undoubtedly or very probably bimolecular are marked with a superscript (2). Those for which the evidence is very strong that the mechanism is wholly or substantially the unimolecular one (including its silver-ion-catalysed modification) are indicated by a superscript (1). The other figures relate to reactions for which the evidence on the whole indicates a mixture of mechanisms, or at least would permit this interpretation.

TABLE IX.

Relative Rates in Bimolecular and Unimolecular Hydrolysis or Alcoholysis.

Bromides.	CH_3.	$CH_3{\cdot}CH_2$.	$MeCH_2{\cdot}CH_2$.	$Me_2CH{\cdot}CH_2$.	$Me_3C{\cdot}CH_2$.
OEt^- in EtOH, 55°	17·6 (2)	1 (2)	0·28 (2)	0·030 (2)	0·0000042 (2)
H_2O–EtOH, "50%," 95°	2·03 (2)	1 (2)	0·58 (2)	0·080	0·0064 (1)
$Ag^+ + H_2O$–EtOH, "70%," 64°	0·81	1	0·55	0·084	0·013 (1)
H_2O–$H{\cdot}CO_2H$, 95°	0·64	1 (1)	0·69 (1)	—	0·57 (1)
Chlorides.	—	$CH_3{\cdot}CMe_2$.	$MeCH_2{\cdot}CMe_2$.	—	$Me_3C{\cdot}CEt_2$.
H_2O–EtOH, "80%," 25°	—	1 (1)	1·76 (1)	—	13·7 (1)

(For the meaning of "50%" and "70%" see pp. 165 and 170.)

The already discussed relationships in the first line are characteristic of the bimolecular mechanism: the steric effect is dominant. It appears that in the *dry* alcoholic solvent the rate of ionisation of primary halides is insufficient to allow the ionisation mechanism to show itself even in the case of *neo*pentyl bromide.* This follows, *inter alia*, because the rate is proportional to the ethoxide concentration, and because the substitution product has a normal *neo*pentyl structure (Parts XXVI and XXIX). In aqueous alcohol the ionisation rate is much greater, sufficiently so to dominate the reaction of *neo*pentyl bromide, the bimolecular substitution of which must be sterically hindered as before. This is deduced because, *inter alia*, added alkali does not increase the rate, and the substitution product has a rearranged carbon structure (Part XXIX). The incursion of an ionisation type of mechanism seems to be carried a little further in the silver reactions, and much further still in the best ionising solvent which it has yet been possible to find for the hydrolysis of alkyl halides, *viz.*, moist formic acid (cf. Bateman and Hughes, J., 1937, 1187; 1940, 935, 940, 945). Here all the rates are of the same order of magnitude, and we assume in consequence that the unimolecular mechanism is important throughout the series. It is likely, however, that the unimolecular rates for methyl, ethyl, and *n*-propyl bromide are smaller than the observed rates, which probably contain a substantial bimolecular contribution (cf. Bateman and Hughes, J., 1940, 940, 945). The theoretical sequence for the polar effect in unimolecular substitution is Me < Et < Pr^n < *iso*Bu < *neo*pentyl, but all the differences, except the first, should be small. One might expect the initial difference Me < Et to be reproduced in the observed rates, as indeed it is in the formic acid solvent. The smaller differences might not be so reproduced, for the reason that we do not measure rates near the absolute zero of temperature, but make observations with vibrating and rotating molecules, rather than the static molecules which implicitly are under consideration when a polar sequence such as the above is written. We do, in fact, observe the correct polar sequence, as can be seen in the last line of the table, in the rates for the tertiary halides, for which the mechanism is indubitably unimolecular, and the theoretical polar effect is enhanced in the last member of the series by the use of α-Et_2 groups. Clearly, the polar effect dominates rate in the unimolecular mechanism; indeed, it is impossible to survey these kinetic relationships comprehensively without reaching the conclusion that steric hindrance plays no appreciable part in the unimolecular substitutions of alkyl halides.

It is an evident consequence of these relations that, for structures which are sterically hindered in bimolecular substitution, more success may sometimes be gained in effecting reaction by the addition of an ionising solvent than by the introduction of a powerfully nucleophilic reagent. For instance, Whitmore took drastic measures with limited success in his attempts to hydrolyse *neo*pentyl halides with reagents such as concentrated alcoholic alkali, although hydrolysis could easily have been effected, without any alkali, by simply adding water

* Experiments which will be published later make it probable that the ionisation rate is between 10 and 100 times too small to make itself felt in these experiments.

to the alcohol. It is true that, in the particular case of *neo*pentyl compounds, substitution by the unimolecular mechanism is accompanied by a rearrangement which, if the object in view were preparative, it might be desired to avoid; but there are many other structures which can be predicted to be subject to marked steric hindrance in bimolecular substitution, and not subject to rearrangement in unimolecular substitution. One example is now being studied, and there will be a later opportunity to discuss it.

2. *Reaction of alcohols.* Reference has already been made (p. 188) to Bartlett and Knox's observation that αα-diethyl*neo*pentyl alcohol is instantaneously converted into the corresponding chloride by dry hydrogen chloride. Setting this fact besides others (this vol., p. 188) relating to the conversion of alcohols into halides, we have already concluded that Bartlett and Knox must have had the unimolecular mechanism, S_N1, under observation. The further conclusion can be drawn that this mechanism also is unaffected by steric hindrance.

3. *Reactions of carboxyl compounds.* Day and Ingold discussed three unimolecular mechanisms of carboxyl esterification and hydrolysis, of which one, involving acid catalysis and acyl–oxygen fission, had been kinetically investigated (by Graham), in the example of benzoic acid and its esters and their nuclear substitution products, in sulphuric acid solvents (*loc. cit.*). The rates of these reactions depend on the slow heterolysis of a rapidly formed oxonium ion $R{\cdot}CO{\cdot}\overset{+}{O}HR'$, to give the carbonylium ion $R{\cdot}\overset{+}{C}O$, which is thereafter rapidly attacked by water or alcohol. Treffers and Hammett first discovered by qualitative observation (*J. Amer. Chem. Soc.*, 1937, **39**, 1708) what has since been confirmed kinetically, *viz.*, that *o*-methyl substitution, which would sterically inhibit any reaction dependent on a bimolecular transition state centred at the carbonyl carbon atom, actually accelerates esterification and hydrolysis in sulphuric acid solvents. Day and Ingold (*loc. cit.*) attributed these results to the polar effect, *i.e.*, to the electron supply, which is needed to assist the formation of the carbonylium ion, and which the *o*- and *p*-methyl groups can furnish; and it was pointed out that there was not, and should not be, any appreciable steric effect.

Summarising, we conclude that, according to the evidence now available, there is no steric effect in *any* unimolecular substitution; and no doubt the reason is that given by Day and Ingold for the case which they were discussing, *viz.*, that, in contrast to the inevitable congestion of the bonds in bimolecular transition states, no new covalencies are being formed in the transition state of an ionisation, the attack on the separating particles being more or less external, and the forces largely of the longer range, electrostatic type.

(d) *Superposed Bimolecular and Unimolecular Mechanisms in Nucleophilic Substitution.*—Although our discussion of the hydrolytic and allied reactions of alkyl halides has referred almost exclusively to various primary and tertiary alkyl halides, the conclusions reached inevitably affect our view of the corresponding reactions of secondary halides. In illustration, we may consider the following comparison of the parameters B and E of the Arrhenius equation, $k_1 = Be^{-E/RT}$, as applied to the solvolytic reactions of a primary and a tertiary alkyl halide in aqueous alcohol. We choose the reactions so that they shall be mechanistically simple and comparable, and therefore take *neo*pentyl bromide as the primary halide, since we can prove that its solvolysis is unimolecular and thus comparable with the demonstrably unimolecular solvolysis of *tert.*-butyl bromide. The following data concerning *neo*pentyl bromide are given in Part XXIX (this vol., p. 166); the figures for *tert.*-butyl bromide are taken from an earlier paper (Bateman, Cooper, Hughes, and Ingold, J., 1940, 925):

Bromide.	Solvent.*	$k_{25°}$ (sec.$^{-1}$).	B (sec.$^{-1}$).	E (kg.-cals.).
*neo*Pentyl	" 50% " EtOH	$8{\cdot}3 \times 10^{-11}$	$1{\cdot}5 \times 10^{11}$	29·0
tert.-Butyl	" 60% " EtOH	$3{\cdot}8 \times 10^{-3}$	$3{\cdot}1 \times 10^{13}$	21·7

* The expression " x% " EtOH means the solvent obtained by mixing at room temperature x vols. of anhydrous ethyl alcohol with $100 - x$ vols. of water.

It will be noticed that the compositions of the aqueous-alcoholic solvents are not the same; but the difference of solvent composition is not important in relation to the large rate differences now under consideration. Judging from data on *neo*pentyl bromide in " 50% " and " 70% " ethyl alcohol, a factor of about 0·4 applied to the rate for *neo*pentyl bromide would make it correspond to the solvent used for *tert.*-butyl bromide. The broad conclusion is that the rate of ionisation of the tertiary bromide is about 10^8 times greater than that of the primary bromide, and that, of this ratio, a factor of about 10^5 is represented by an increase in the Arrhenius parameter B, whilst the complementary factor arises from a decrease of activation energy, amounting to about 7 kg.-cals.

It seems a reasonable assumption in the light of these data that if we could obtain a pure unimolecular solvolysis, S_N1, of a secondary alkyl bromide in aqueous alcohol, the rate should be about 10^4 times smaller than for the *tert.*-butyl bromide, and the Arrhenius activation energy should be about 25—26 kg.-cals. Now Cooper, Hughes, and Shapiro showed (J., 1937, 1177, 1183) that the rates of solvolysis of the *iso*propyl halides in aqueous alcohol are in fact about 10^4 times smaller than for the corresponding *tert.*-butyl halides. The puzzling feature was, however, that the differences from the *tert.*-butyl halides were mainly represented by reduced B-factors, and not to any large extent by increased E-values. At that time (1937) the solvolysis of secondary halides was regarded as mechanistically marginal, but as following mainly the unimolecular process (S_N1). The marginal nature of these reactions has been consistently evident, but in 1940 Bateman, Cooper, Hughes, and Ingold (*loc. cit.*), as a result of considering the sensitivity of the rate of substitution to solvent composition, and to dissolved nucleophilic anions, concluded that a large part of the observed solvolytic rate was probably that of the bimolecular process (S_N2). Our new work shows that Cooper, Hughes, and Shapiro's

results can be fitted into this revised picture of the reaction. The observed rates could be 10^4 times smaller than for *tert.*-butyl halides if a unimolecular rate of this order were overlaid by a bimolecular rate which could be smaller, or up to two or three times larger, but should not be of a larger order of magnitude. But if the bimolecular contribution to the total reaction were the larger, then the Arrhenius activation energy would approximate more closely to the activation energy of a bimolecular solvolytic substitution S_N2, than to that of a unimolecular substitution S_N1. It is true that we do not exactly know the activation energies of S_N2 solvolyses; but the reaction consists in the attack of a neutral molecule, H_2O or ROH, on an alkyl halide; and analogy with the Menschutkin reaction (involving attack by neutral R_3N, etc., on an alkyl halide), which belongs to the same sub-class of nucleophilic substitutions and has been the subject of many kinetic investigations, suggests low values, probably not much above 20 kg.-cals. The apparent activation energy for the solvolysis of *iso*propyl bromide should fall between this not accurately known lower limit for an S_N2 reaction, and an upper limit of about 25—26 kg.-cals. corresponding to the S_N1 reaction; indeed, according to Bateman, Cooper, Hughes, and Ingold's revised view of the mechanistic constitution of the reaction, its activation energy should lie nearer the lower limit. The observed value, 22·7 kg.-cals., tends to confirm this revised view against the opinion which had earlier prevailed.

Data are on record which show that the same type of view applies to the solvolysis of *iso*propyl chloride and iodide (Cooper, Hughes, and Shapiro, *loc. cit.*), and also to the solvolysis of other simple secondary alkyl halides, such as β-*n*-octyl chloride, bromide and iodide (Hughes and Shapiro, J., 1937, 1192). In all these cases a fairly large part of the reaction in aqueous alcohol is bimolecular. The exact proportions we do not yet know, but it will be evident that the foregoing discussion provides the principles of a method, which we are even now proceeding to apply, for the quantitative mechanistic analysis of solvolytic reactions of mixed molecularity. We require, as reference data, the activation energies of solvolysis of pure S_N1 and S_N2 mechanisms. For the S_N1 reaction we can use, *e.g.*, α-methyl*neo*pentyl bromide, since the *neo*pentyl group will ensure the absence of the bimolecular process; and the result will apply to secondary alphyl bromides generally, because there is no steric effect in unimolecular substitutions (sub-division *c* of division *B*) and the polar effect of β-methyl groups is in first approximation negligible (sub-division *b*). For S_N2 solvolysis in aqueous alcohol, methyl bromide is a safe choice. For this case small corrections for both polar and steric factors are necessary in order to obtain a value appropriate to secondary alphyl bromides; but we have already illustrated (division *A* of this paper) how, by a combination of experiment and calculation, such corrections might be estimated.

It is a consequence of the revised picture of the mechanistic constitution of the solvolytic reactions of secondary alphyl halides that the degree of racemisation accompanying *a strictly unimolecular* solvolysis of optically active secondary halides must be more extensive than was at first inferred from the experimental data on the assumption that most of the observed reaction was unimolecular (Hughes, Ingold, and Masterman, J., 1937, 1196). We hope to make a quantitative assessment of the degree of racemisation by associating mechanistic analyses on the lines indicated above with studies of the changes of optical rotatory power.

It will be appreciated that, in contrast to the differences of activation energy in S_N2 substitutions, an important part of which is due to steric hindrance, the drop of 7 kg.-cals. in the activation energy of S_N1 substitutions, on passing from primary, through secondary, to tertiary alkyl groups, is to be regarded as a pure polar effect. Part of it will be inductometric and part electromeric. The inductometric part is of an electrostatic nature, and can be shown by calculation to be of magnitude sufficient to account for a substantial part of the observed energy difference. The electromeric part depends on the energy of hyperconjugation between the alkyl branches and the breaking C–Br bond, $H_3C\overset{\curvearrowright}{—}C\ldots\overset{\curvearrowright}{Br}$; and it might also be considerable, since we know that in systems such as $H_3C\overset{\curvearrowright}{—}C_6H_4\overset{\curvearrowright}{—}C\ldots Cl$ hyperconjugation energies may amount to several kg.-cals. (Hughes, Ingold, and Taher, J., 1940, 949). Further discussion of this matter is deferred, since the quantitative calculation of polar effects requires a separate paper for its development.

(C) *The Wagner Rearrangement in Relation to Unimolecular Mechanisms of Substitution and Elimination* (S_N1 and $E1$).

(a) *Ionisation a Preliminary to Rearrangement.*—The work of Whitmore and his associates, extended, as it has been, in one direction by Kharasch and in others by ourselves, on the reactions of *neo*pentyl halides and analogous compounds, forms a basis for assessing the position of that class of rearrangements of which the Wagner change is typical, in relation to the mechanisms of substitution and elimination which we have been studying for several years.

The following four statements concerning the Wagner change in this group of examples can be made on the basis of the evidence mentioned. Statements (1) and (2) follow from Whitmore's work and ours, taken together, on certain reactions of *neo*pentyl compounds (Whitmore and Rothrock, *J. Amer. Chem. Soc.*, 1932, **54**, 3431; Whitmore and Fleming, *ibid.*, 1933, **55**, 4161; Whitmore, Wittle, and Popkin, *ibid.*, 1939, **61**, 1586; the preceding six papers by Dostrovsky and Hughes; division *B* of this paper). Statement (3) has been established by Whitmore (Whitmore and Fleming, *loc. cit.*; Whitmore, Wittle, and Harriman, *ibid.*, 1939, **61**, 1585; cf. Whitmore and Zook, *ibid.*, 1942, **64**, 1783). Statement (4) has been denied by Whitmore (cf. Whitmore, Popkin, Bernstein, and Wilkins, *ibid.*, 1941, **63**, 124; Whitmore and Zook, *loc. cit.*), even though,

in his work on " neophyl " compounds (having the group $CPhMe_2 \cdot CH_2 \cdot$), he has provided some of the evidence in favour of it (Whitmore, Weisgerber, and Shabiea, *ibid.*, 1943, **45**, 1469); its truth has been well established by Urry and Kharasch (*ibid.*, 1944, **66**, 1436).

(1) No rearrangement of the carbon skeleton occurs in those reactions of *neo*pentyl compounds in which the *neo*pentyl group remains covalently bound continuously throughout the process. (The bimolecular ethoxylation of *neo*pentyl bromide by sodium ethoxide is an example.)

(2) Rearrangement to the *tert.*-amyl structure always takes place in reactions in the course of which the *neo*pentyl group is liberated as a cation. (The main examples are the unimolecular nucleophilic substitutions and eliminations, with rearrangement, and the allied heterogeneous reactions, of *neo*pentyl halides to give, *e.g.*, *tert.*-amyl alcohol or ethyl *tert.*-amyl ether, and trimethylethylene.)

(3) No rearrangement takes place in those reactions of *neo*pentyl compounds in the course of which the *neo*pentyl group becomes converted into an anion. (Electrophilic substitutions, proceeding by an ionic mechanism, have been illustrated by the conversion of *neo*pentyl-metal compounds into halides, *e.g.*, the conversion of *neo*pentylmercuric chloride into *neo*pentyl iodide by the action of iodine.)

(4) Rearrangement occurs in those reactions of neophyl compounds in the course of which the neophyl group is liberated as a neutral radical. (This is the case in homolytic * substitutions and eliminations, as exemplified by the conversion of neophyl chloride, with migration of the phenyl group, into *iso*butylbenzene and ββ-dimethylstyrene, under the conditions of the Würtz reaction, or through the use of phenylmagnesium bromide together with cobaltous chloride.)

These four statements can obviously be generalised and condensed into a single statement: It is a necessary condition for the Wagner rearrangement that substitution or elimination should proceed through a *carbon cation or radical*—in either case, through an entity with an incomplete carbon octet.

Ingold and Shoppee originally classified the pinacol–pinacolin and Wagner rearrangements with elimination reactions (J., 1928, 365; cf. Shoppee, *Proc. Leeds Phil. Soc.*, 1928, **1**, 301), though Ingold stressed the formation of a carbonium ion (*Ann. Reports*, 1928, **25**, 133).† It now appears that, so far as the class of heterolytic reactions is concerned, these rearrangements should be associated with the *unimolecular nucleophilic substitutions and eliminations*, S_N1 *and* E1, which have only since that time been recognised. Isomeric changes are automatically included as " symmetrical " unimolecular substitutions (cf. p. 175, footnote).

The condition for rearrangement, stated above as necessary, is not sufficient; for the formed cation or radical might be more stable than any isomeride it could produce by rearrangement. The important factor here is the resonance energy between the groups present and the carbonium ionic or radical centre in its various possible positions. Thus $CMe_3 \cdot \overset{+}{C}H_2$ rearranges, $CMe_3 \cdot \overset{+}{C}HPh$ does not, and $CPh_3 \cdot \overset{+}{C}HPh$ does (Skell and Hauser, *J. Amer. Chem. Soc.*, 1942, **64**, 2633). These facts illustrate the importance of hyperconjugation, $H_3C\overset{\curvearrowright}{—}\overset{+}{C}$, and the greater importance of conjugation, $Ph\overset{\curvearrowright}{—}\overset{+}{C}$, as factors of stability.

The migrating group moves *with* its shared electrons, *e.g.*, $Me_2C(-Me) \cdot \overset{+}{C}H_2 \longrightarrow Me_2\overset{+}{C} \cdot CH_2(-Me)$: these electrons must be vitally concerned in establishing the link with the original position of the carbonium or radical centre. Accordingly, Shoppee's rule (see Baker, " Tautomerism," Chapter XIV, Routledge, 1934) seems quite reasonable—that, when alternative groups might migrate from a given carbon atom to its neighbour, that group will preferentially migrate which can develop the greatest electron density at the point of its attachment (*e.g.*, anisyl > phenyl > methyl).

Whether or not rearrangement occurs in a formed carbonium ion, two sequelæ are normal: the carbonium ion either adds an anion or loses a proton: the result is either unimolecular nucleophilic substitution, S_N1, or unimolecular elimination, *E*1, or the modified forms of these processes involving rearrangement.

When the place, which in the preceding discussion is accorded to a carbon cation, is taken by a nitrogen cation with an open sextet, we obtain a picture of the Hofmann, Lossen, Curtius, and Beckmann rearrangements,‡ as Whitmore has already recognised (*J. Amer. Chem. Soc.*, 1932, **54**, 3274). Although Whitmore has objected to being associated with " ionic " mechanisms of rearrangement (Whitmore and Fleming, J., 1934, 1269), it seems to us that no one has done more than he to establish such mechanisms.§

* " Homolytic " reactions are those in which the bonds break according to the scheme A.|.B. The reactions of classes (1), (2), and (3) are " heterolytic "; *i.e.*, the bonds break thus, A|..B (the dots represent electrons).

† Though we do not summarise the earlier history, it is impossible not to mention that Meerwein's work first suggested the importance of ionisation in the Wagner change.

‡ These four rearrangements are often described as " intramolecular " on the evidence of preserved configurations in suitable optically active compounds. But they are just as truly " extramolecular ": it all depends on which of the two interchanging groups one is thinking about. In the Wagner change, $R{-}C_\alpha{-}C_\beta{-}X \longrightarrow X{-}C_\alpha{-}C_\beta{-}R$, group X separates as X^-, then R migrates internally, and then X returns externally, unless it is eliminated; so that the original configuration about C_β becomes lost, whilst configurations in R are preserved. Similarly, in the Hofmann, Lossen, Curtius, and Beckmann rearrangements, X in $R{-}C_\alpha{-}N{-}X$ or $R{-}C_\alpha{=}N{-}X$ separates as $\overline{X}$, R migrates internally and X returns if it is not eliminated. Only configurations within R have yet been tested with respect to their optical stability.

§ In the substitutions with rearrangement of *neo*pentyl halides studied by Whitmore, the halogen was generally removed by an added reagent such as a silver salt, whilst we have achieved the same chemical result in suitable solvents without any such addition. Probably it was the particular range of his experience that led Whitmore to reject the ionic interpretation. In our picture the silver ion is an electrophilic catalyst for ionisation (Cowdrey, Hughes, Ingold, Masterman, and Scott, J., 1937, 1252; Bateman, Cooper, Hughes, and Ingold, J., 1940, 930).

(b) *Rearrangement as a Sequel to Ionisation.*—Rearrangement is not essential to the formation of a carbonium ion, for many well-established carbon ionisations do not involve rearrangement. Nevertheless, the question has been raised as to whether, when rearrangement does occur, it accompanies or succeeds the ionisation (Skell and Hauser, *loc. cit.*). The life of a *neo*pentyl cation, before its rearrangement to the *tert.*-amyl cation, must be very short, because it yields no detected substitution products with an unrearranged *neo*pentyl structure. The question is whether the lives of such unrearranged cations are in general and in principle too brief to be significant for reactions. It is not an answer to point out that some other carbonium ions yield unrearranged and rearranged substitution products side by side: mesomeric ions do that, and their canonical forms are universally believed not to exist as separate chemical entities. General evidence of a really unequivocal kind seems, indeed, very difficult to obtain; but we know of one case in which a special stereochemical situation discloses the answer.

This is the conversion, already cited by Bateman, Cooper, Hughes, and Ingold (*loc. cit.*), of camphene hydrochloride into *iso*bornyl chloride, a reaction which has been intensively studied by means of several tools, including kinetics, optical activity, and hydrogen and chlorine isotopic indicators. There is plenty of evidence that the initial stage is a rate-controlling ionisation of the chlorine atom. A possible route would therefore be: camphene hydrochloride ⟶ " camphene hydro- " cation ⟶ bornyl cation ⟶ *iso*bornyl chloride. The original question, as applied to this case, is whether the " camphene hydro- " cation has a separate existence, or whether, on the other hand, the camphene hydrochloride ionises and rearranges " all at once " to give the bornyl cation directly. The answer is known, and is unequivocal: it is the bornyl cation which has no separate existence in this chain of reactions. This follows because the stereochemical difference between bornyl and *iso*bornyl chloride disappears in the bornyl cation; which, when it *is* formed, and subsequently associated with a chloride ion, produces bornyl, not *iso*bornyl, chloride. Here then, it is clear that, although the reaction proceeds to give rearranged products almost completely, the unrearranged cation is the only one which exists long enough to enter into reaction. It has been shown that this cation needs the presence of a chloride ion in order to undergo the rearrangement of structure (*idem, ibid.*).

We are much indebted to the Department of Scientific and Industrial Research for their financial support of the work described in this group of papers, and to the Chemical Society and Imperial Chemical Industries Ltd. for providing some of the materials required. Part of the work was carried out at Aberystwyth in the laboratories of Professor T. Campbell James, whom we wish to thank for his hospitality.

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[*Received, August 28th,* 1945.]

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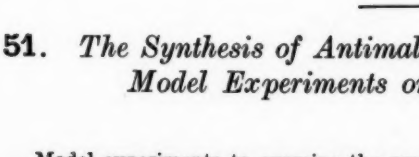
51. *The Synthesis of Antimalarial Compounds Related to Niquidine. Part I. Model Experiments on the Synthesis of Quinolyl Carbinols.*

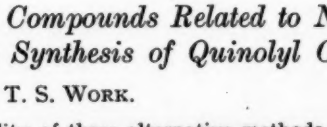
By T. S. WORK.

Model experiments to examine the practicability of three alternative methods for the synthesis of compounds of niquidine type are described. Condensation of a quinoline-4-aldehyde with a 3-ketopiperidine without elimination of water was successfully achieved but the keto group could not be reduced. Condensation of an aliphatic aldehyde with a 4-acetylquinoline gave an unsaturated ketone which was reduced to a quinolylalkylcarbinol. Condensation of a quinoline-4-aldehyde with aliphatic nitro-compounds gave nitro-hydroxy-derivatives of quinoline reducible to aminoquinolyl-carbinols. α-Piperidyl-6-methoxy-4-quinolylcarbinol was synthesised by this method.

NIQUIDINE, a degradation product of quinidine, has been reported (Buttle, Henry, Solomon, Trevan and Gibbs, *Biochem. J.*, **1938**, **32**, 47) to be more active than quinine in bird malaria. On the basis of degradative experiments, structure (I) was assigned by Gibbs and Henry (*J.*, **1939**, 240) to niquidine.



(I.)



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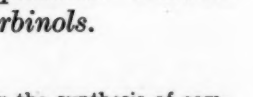
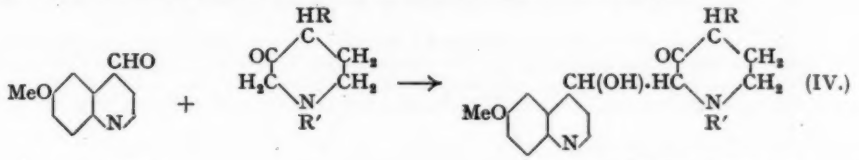


(III.)

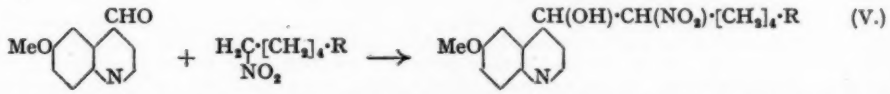
Ainley and King (*Proc. Roy. Soc.*, **1938**, **125**, B, 60) synthesised α-piperidyl-6-methoxy-4-quinolylcarbinol which may be regarded as niquidine with the unsaturated side-chain removed. This compound was rather less active than quinine in bird malaria. To study the effect of simplifying the " quinuclidine half " of the quinine molecule still further, King and Work (*J.*, **1940**, **1307**) synthesised a series of 6-methoxy-4-quinolyldialkylaminomethyl-carbinols (II). They found that, in a homologous series (R = methyl to R = heptyl), activity reached a peak at dibutylamino or diamylamino but that the most active member of the series was no more active than α-piperidyl-6-methoxy-4-quinolylcarbinol despite closer similarity to quinine in molecular weight. These results indicated that it might be more profitable to study the synthesis of α-piperidylquinolylcarbinols with suitable alkyl or alkenyl substituents in the piperidine ring.

Clearly such a synthesis might be possible starting from quininic ester and alkylpiperidines using the method of Ainley and King (*loc. cit.*), but as the higher alkylpiperidines are not readily obtainable and as the overall yield by this method was not high it was considered worth while to study alternative methods for linking the quinoline half of the molecule with suitable bases.

Three possible routes have been studied : (i) condensation of 6-methoxy-4-acetoquinoline with aldehydes to give unsaturated ketones; (ii) condensation of 6-methoxyquinoline-4-aldehyde with 3-ketopiperidines; and (iii) condensation of 6-methoxyquinoline-4-aldehyde with suitable nitro compounds.



(IV.)

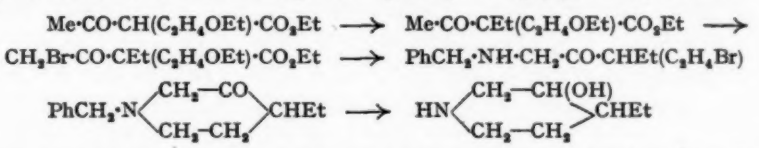


(V.)

As a suitable model for (i), butyraldehyde was successfully condensed with 6-methoxy-4-acetoquinoline using alcoholic potassium hydroxide as a condensing agent to give 6-methoxy-4-quinolyl pentenyl ketone, (III; R = C_3H_7), isolated as the *picrate*.

To extend this synthesis to compounds of the niquidine type phenoxyethylvaleraldehyde was condensed with 6-methoxy-4-acetoquinoline by this method (see following paper).

The practicability of (ii) was examined by synthesising *3-keto-N-benzyl-4-ethylpiperidine* by the following series of reactions : *ethyl α-(β'-ethoxyethyl)acetoacetate* was alkylated with ethyl iodide to give *ethyl α-ethyl-α-(β'-ethoxyethyl)acetoacetate* which was brominated to give *ethyl γ-bromo-α-ethyl-α-(β'-ethoxyethyl)acetoacetate*; the latter was condensed with benzylamine and hydrolysed with hydrobromic acid to give *benzyl-(ε-bromo-β-keto-γ-ethylamyl)amine hydrobromide*; this on treatment with alkali gave the desired *3-keto-N-benzyl-4-ethylpiperidine*. Catalytic reduction of this base gave 3-hydroxy-4-ethylpiperidine, thus :



Condensation of 6-methoxyquinoline-4-aldehyde and 3-keto-*N*-benzyl-4-ethylpiperidine in presence of sodium methoxide yielded *α-(3-keto-N-benzyl-4-ethyl)piperidyl-6-methoxy-4-quinolylcarbinol* (IV; R = Et, R' = CH_2Ph), but it was not found possible to reduce the keto to a methylene group (cf. Clemo and Hoggarth, *J.*, 1939, 1241).

As a model for (iii) 6-methoxyquinoline-4-aldehyde was condensed with nitrobutane using sodium methoxide as a condensing agent : *6-methoxy-4-quinolyl-α-nitrobutylcarbinol* was obtained in fairly good yield and it was reduced catalytically to 6-methoxy-4-quinolyl-α-aminobutylcarbinol isolated as the *dihydrobromide*. To extend this method to the synthesis of piperidylquinolyl-carbinols, *ε-nitroamyl benzoate*, synthesised from ε-bromoamyl benzoate, was condensed with 6-methoxyquinoline-4-aldehyde and the product catalytically reduced to give *6-methoxy-4-quinolyl-(α-amino-ε-benzoxyamyl)carbinol* (as V; R = $PhCO_2$). This base could not be cyclised to the desired piperidine so the method was modified by using *α-bromo-ε-nitropentane* in place of ε-nitroamyl benzoate, bromonitropentane being obtained from αε-dibromopentane by controlled reaction with silver nitrite.

α-Bromo-ε-nitropentane with the bisulphite compound of 6-methoxyquinoline-4-aldehyde and sodium ethoxide (cf. U.S.P. 2,151,517) gave a good yield of *6-methoxy-4-quinolyl-(ε-bromo-α-nitroamyl)carbinol* (V; R = Br). The two externally compensated forms of this compound were separated by fractional crystallisation and reduced catalytically. The yields of the desired α-piperidyl-6-methoxy-4-quinolyl-carbinols were not good owing, apparently, to partial reduction of the ε-bromo group before cyclisation, but both externally compensated forms of the piperidyl carbinol were obtained for comparison with specimens prepared by Ainley and King (*loc. cit.*). One isomeride melted at 166° and was probably identical with that prepared by Ainley and King. The second isomeride melted at 181° and appeared to differ from that reported by Ainley and King.

By the application of this method to a suitably substituted nitropentane, a compound having the structure assigned by Henry and Gibbs (*loc. cit.*) to dihydroniquidine has been synthesised. (See following paper.)

αε-Dinitropentane, available as a by-product in the preparation of bromonitropentane, condensed in the same way with 6-methoxyquinoline-4-aldehyde to give *6-methoxy-4-quinolyl-αε-dinitroamylcarbinol* (V; R = NO_2), which was reduced to the corresponding amine isolated as *6-methoxy-4-quinolyl-αε-diaminoamylcarbinol trihydrochloride*. In contrast with the corresponding cyclised base, this compound had no antimalarial properties.

Experimental.

Ethyl α-(β'-Ethoxyethyl)acetoacetate.—To ethyl acetoacetate (150 g.) and sodium ethoxide (25 g. Na) in boiling alcohol bromomethyl ether (150 g.) was added slowly. After boiling for twenty-four hours, alcohol was removed and the cooled mixture acidified. The separated product was fractionally distilled under reduced pressure and the fraction (118 g.), b. p. 118—120°/11 mm., was collected (Found: C, 59·4; H, 8·9. $C_{10}H_{18}O_4$ requires C, 59·4; H, 8·9%).

Ethyl α-Ethyl-α-(β'-ethoxyethyl)acetoacetate.—Sodamide (22·6 g.) was added to a solution of the above ethyl ethoxyethylacetoacetate (117 g.) in benzene (300 c.c.) and, when the initial reaction was complete, ethyl iodide (90·6 g.) was added and the solution refluxed for eight hours. The product, isolated in the usual way, was fractionally distilled at reduced pressure and the fraction (91·5 g.), b. p. 132—134°/12 mm., was collected (Found: C, 62·9; H, 9·5. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·5%).

Ethyl γ-Bromo-α-ethyl-α-(β'-ethoxyethyl)acetoacetate.—To the product from the above preparation (60 g.) in dry chloroform (750 c.c.) was added slowly dry bromine (42 g.) in chloroform (300 c.c.) with stirring and in absence of moisture. The product in chloroform was washed with sodium bicarbonate solution and the solvent removed. The residual oil was distilled and the fraction (60·4 g.), b. p. 142—148°/3 mm., was collected (Found: C, 46·5; H, 7·0. $C_{12}H_{21}O_4Br$ requires C, 46·6; H, 6·8%).

Benzyl-(ε-bromo-β-keto-γ-ethylamyl)amine.—To a solution of ethyl γ-bromo-α-ethyl-α-ethoxyethylacetoacetate (38·4 g.) in dry ether (150 c.c.) a solution of benzylamine (38 g.) in ether (150 c.c.) was added and the mixture left in darkness for 70 hours. Benzylamine hydrobromide (21·1 g.) was collected and the ether solution washed with sodium carbonate. The product was extracted into dilute hydrochloric acid from the ether and liberated by addition of alkali. This oil (35·7 g.) was boiled for four hours with a mixture of hydrobromic acid (45 c.c., *d* 1·7) and glacial acetic acid (150 c.c.). Charcoal was then added to clear the solution, solvent removed under reduced pressure and the residual gum dissolved in 1% hydrobromic acid (800 c.c.), the small insoluble residue being discarded. The product, from the concentration of the solution, crystallised. After crystallisation from aqueous alcohol the *hydrobromide* (26·7 g.) had m. p. 127° (Found: C, 44·4; H, 5·5; Br, 41·6. $C_{14}H_{20}ONBr,HBr$ requires C, 44·3; H, 5·5; Br, 42·2%).

3-*Keto*-N-*benzyl*-4-*ethylpiperidine.*—The crystalline hydrobromide from the previous preparation (20 g.) was suspended in saturated sodium bicarbonate solution and shaken continuously for 24 hours. The *product* was taken up in ether and fractionally distilled under reduced pressure. The fraction (11 g.), b. p. 124°/7 mm., was collected (Found: C, 77·3; H, 8·7; N, 6·3. $C_{14}H_{19}ON$ requires C, 77·4; H, 8·7; N, 6·4%). The base gave a crystalline *picrate*, needles, m. p. 129° (Found: C, 54·1; H, 5·0. $C_{14}H_{19}ON,C_6H_3O_7N_3$ requires C, 53·9; H, 4·9%).

3-*Hydroxy*-4-*ethylpiperidine.*—3-Keto-*N*-benzyl-4-ethylpiperidine was reduced at normal pressure in aqueous alcohol with Adams' platinum oxide catalyst. The basic product was isolated as a *picrate*, m. p. 138°, which crystallised as needles from methanol (Found: C, 44·2; H, 5·3; N, 15·2. $C_7H_{15}ON,C_6H_3O_7N_3$ requires C, 43·6; H, 5·0; N, 15·6%).

α-3-*Keto*-N-*benzyl*-4-*ethylpiperidyl*-6-*methoxy*-4-*quinolylcarbinol.*—To a solution of 6-methoxyquinoline-4-aldehyde (4·8 g.) and 3-keto-*N*-benzyl-4-ethylpiperidine (5·6 g.) in methanol (10 c.c.) a solution of sodium methoxide (11·3 c.c. containing 0·05 g. sodium per c.c.) was added during one hour. The mixture after 20 hours at 37° was poured into water and the water insoluble fraction taken up in ether. The *base* was taken into acid from ether, liberated by excess alkali and re-extracted with ether. The ether extract (3·5 g.) after removal of solvent crystallised slowly when triturated with benzene and, when pure, had m. p. 127° (Found: C, 74·4; H, 7·0. $C_{25}H_{28}O_3N_2$ requires C, 74·3; H, 6·9%). A crystalline *monopicrate* had m. p. 175° (Found: C, 58·7; H, 5·1; N, 10·9. $C_{25}H_{28}O_3N_2,C_6H_3O_7N_3$ requires C, 58·8; H, 4·9; N, 11·1%).

6-*Methoxy*-4-*quinolyl*-α-*nitrobutylcarbinol.*—α-Nitrobutane (1·03 g.) and 6-methoxyquinoline-4-aldehyde (1·87 g.) were dissolved in alcohol (5 c.c.) and sodium methoxide (4·4 c.c. containing 0·05 g. Na per c.c.) was added very slowly, the mixture warmed to 50° for 5 minutes and then poured into water. The aqueous solution was washed with ether and acidified with dilute acetic acid. The *product* (1·65 g.) after crystallisation from benzene melted at 148° (Found: C, 62·4; H, 6·1; N, 9·7. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·6%). An isomer was present in a subsequent experiment but was not obtained in a pure state.

6-*Methoxy*-4-*quinolyl*-α-*aminobutylcarbinol.*—The product from the above preparation was reduced catalytically in ethanol using Adams' platinum oxide. The product crystallised from alcohol in needles as the *dihydrobromide*, m. p. 230° (decomp.) (Found: C, 42·9; H, 5·3; Br, 38·4. $C_{15}H_{20}O_2N_2,2HBr$ requires C, 42·7; H, 5·2; Br, 37·9%).

ε-*Nitroamyl Benzoate.*—Powdered silver nitrite (14·0 g.) was added slowly with stirring during eight hours to ε-bromoamyl benzoate (20·8 g.) at room temperature; the temperature was then raised to 70—80° and stirring continued for four hours. The silver bromide was separated and the *product* fractionated twice under reduced pressure giving the fraction (10·4 g.) having b. p. 170°/1 mm. (Found: C, 60·5; H, 6·4; N, 6·0. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·3; N, 5·9%).

6-*Methoxy*-4-*quinolyl*-(α-*amino*-ε-*benzoxyamyl*)*carbinol.*—ε-Nitroamyl benzoate (2·37 g.) was added to solution of sodium ethoxide (0·23 g. sodium) in ethyl alcohol at 0° and, after shaking for thirty seconds, was added rapidly to an aqueous solution of the bisulphite compound of 6-methoxyquinoline-4-aldehyde maintained at a temperature of 50°. The mixture was agitated vigorously for 20 minutes, the precipitated oil extracted with benzene, the benzene washed with dilute bisulphite and then with sodium bicarbonate and the solvent removed. The residual oil was dissolved in methanol and reduced in hydrogen at a pressure of 5 atmospheres in the presence of Raney nickel with carbon dioxide as a buffer (cf. U.S.P. 2,157,391). The product was isolated as a *hydrochloride* (0·9 g.) which on crystallisation from alcohol separated as needles melting with decomposition between 190° and 200° (Found: C, 59·7; H, 6·3; N, 6·2; Cl, 15·3. $C_{23}H_{26}O_4N_2,2HCl$ requires C, 59·1; H, 6·1; N, 6·0; Cl, 15·2%). The *base* crystallised with difficulty from ether and had m. p. 64—66° (Found: C, 70·3; H, 6·6. $C_{23}H_{26}O_4N_2$ requires C, 70·1; H, 6·6%).

α-*Bromo*-ε-*nitropentane.*—To αε-dibromopentane (57 g.) in a flask fitted with a high-speed stirrer was added, in small lots, powdered freshly prepared silver nitrite (18 g.) during 3 hours. The reaction was allowed to proceed for a further 48 hours at room temperature and the product fractionally distilled at 15 mm. The first fraction (110—118°) (29·33 g.) was dibromopentane. The intermediate fraction (118—128°) (3·7 g.) was discarded and the final fraction (128—148°) was refractionated and the *distillate* collected between 140—144° (10·0 g.) (Found: N, 7·2. $C_5H_{10}O_2NBr$ requires N, 7·2%).

6-*Methoxy*-4-*quinolyl*-(ε-*bromo*-α-*nitroamyl*)*carbinol.*—6-Methoxyquinoline-4-aldehyde (2·2 g.) dissolved in methanol was added to an excess of aqueous sodium bisulphite and the crystalline product collected. This was suspended in water at 40° and to the suspension was added a solution of bromonitropentane (2·4 g.) in alcoholic sodium oxide (2 mols. Na) at 0°. The mixture was shaken vigorously for 30 minutes and the solid collected. Crystallisation from chloroform gave a product, m. p. 130—140°, which was fractionally crystallised from chloroform–ether, two isomeric nitro compounds being isolated; one (1·3 g.) (m. p. 158°) was sparingly and the other (0·65 g.) (m. p. 136—137°) was readily soluble in cold chloroform (Found: C, 50·1; H, 5·0; N, 7·3; Br, 20·7. $C_{16}H_{19}O_4N_2Br$ requires C, 50·1; H, 5·0; N, 7·3; Br, 20·9%).

α-*Piperidyl*-6-*methoxy*-4-*quinolylcarbinol.*—Both isomers were reduced in the same way. The methoxyquinolyl-

bromonitroamylcarbinol was dissolved in methanol, solid CO_2 added, and reduction effected by hydrogen at 5 atms. with Raney nickel catalyst. After removal of the catalyst the product was isolated as a crystalline base. The isomer having m. p. 158° gave a base, m. p. 181°, and the isomer having m. p. 136° gave an isomeric base, m. p. 166°, which, mixed with a specimen of the same base (m. p. 164°) prepared by the method of Ainley and King, gave no depression of the m. p.

6-Methoxy-4-quinolyl-αε-dinitroamylcarbinol.—αε-Dinitropentane was condensed with the bisulphite compound of 6-methoxyquinoline-4-aldehyde by the method described above. The solid product crystallised from alcohol but, although two isomers were obviously present, only one of these, m. p. 163°, was obtained pure; after numerous fractional crystallisations the final *product* separated as sparingly soluble platelets from alcohol (1·1 g.) (Found: C, 55·3; H, 5·4; N, 11·7. $C_{16}H_{19}O_6N_3$ requires C, 55·0; H, 5·4; N, 12·0%).

6-Methoxy-4-quinolyl-αε-diaminoamylcarbinol.—The methoxyquinolyldinitroamylcarbinol was reduced by hydrogen at 5 atms. with Raney nickel as catalyst in the presence of carbon dioxide, an 80% yield being obtained. Methoxyquinolyldiaminoamylcarbinol was isolated as the *trihydrochloride*, m. p. 226° (decomp.), which crystallised as fine needles from methanol–acetone (Found: C, 47·9; H, 6·6; N, 9·6. $C_{16}H_{23}O_2N_3,3HCl$ requires C, 48·2; H, 6·5; N, 10·5%).

6-Methoxy-4-quinolyl Pentenyl Ketone.—6-Methoxy-4-acetylquinoline (1 g.) in alcoholic potassium hydroxide (5 c.c., 5%) was heated to 70° in a flask fitted with reflux condenser, and butyraldehyde (0·36 g.) in alcohol (5 c.c.) was run into the solution. The mixture was boiled for ten minutes, cooled and poured into hydrochloric acid (100 c.c., 1%). The acid was washed with ether and the base liberated by excess alkali. The base (0·7 g.) could not be crystallised but gave a crystalline *picrate*, m. p. 218°, sparingly soluble in cold acetone (Found: C, 54·6; H, 4·3; N, 11·0. $C_{16}H_{17}O_2N,C_6H_3O_7N_3$ requires C, 54·5; H, 4·1; N, 11·6%).

I wish to thank Mr. N. Schunman for technical assistance.

NATIONAL INSTITUTE FOR MEDICAL RESEARCH, LONDON, N.W.3. [*Received, November 19th*, 1945.]

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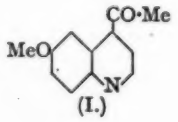
52. *The Synthesis of Antimalarial Compounds Related to Niquidine. Part II. Synthesis of a Dihydro-x-niquidine.*

By T. S. WORK.

A synthesis of dihydro-*x*-niquidine has been developed. Condensation of 6-methoxyquinoline-4-aldehyde (IV) with 5-bromo-1-nitro-3-propylpentane (V) gave (VI) which on reduction cyclised spontaneously to give dihydroniquidine (VII). Only one of the four possible racemates was obtained pure. Synthetic dihydroniquidine was found to be a highly active antimalarial.

An alternative synthesis, suggested by preliminary experiments (Part I), the condensation of alkoxyethylvaleraldehydes (II) with 6-methoxy-4-quinolyl methyl ketone (I) was abandoned owing to the impossibility of purifying the product (III).

IN Part I (previous paper) general methods for linking the quinoline and piperidine " halves " of the niquidine structure were studied. In order to extend these methods to the synthesis of dihydroniquidine it was necessary to devise methods for the preparation of α(β′-alkoxyethyl)valeraldehyde (II) and *5-bromo-1-nitro-3-propylpentane* (V).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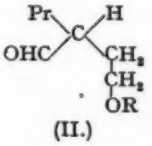
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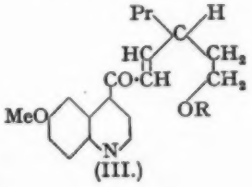
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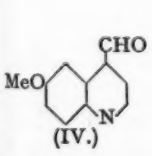
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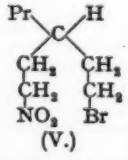
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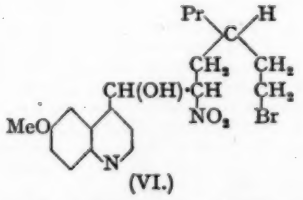
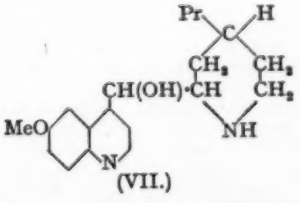
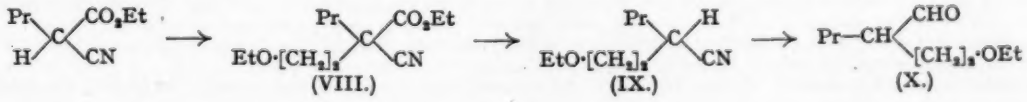

(VI.)


(VII.)

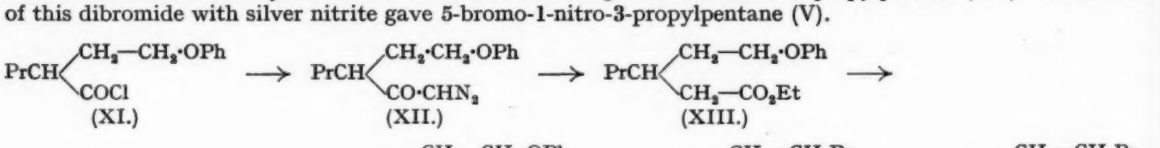
Ethyl propylcyanoacetate condensed with β-ethoxyethyl bromide to give *ethyl α(β′-ethoxyethyl)propylcyanoacetate* (VIII). Hydrolysis of the ester gave *α(β′-ethoxyethyl)propylcyanoacetic acid* which distilled at low pressure without decarboxylation. Decarboxylation was achieved by distilling slowly at normal pressure to give *α(β′-ethoxyethyl)valeronitrile* (IX). Application of the stannous chloride method of Stephen (*J.*, 1925, 1874) converted this nitrile in rather poor yield into α(β′-ethoxyethyl)valeraldehyde (X) isolated as its 2 : 4-*dinitrophenylhydrazone*.


(VIII.) (IX.) (X.)

In the hope of obtaining a better overall yield of the desired aldehyde, ethyl propylmalonate was allowed to react in the same way with β-ethoxyethyl bromide to give *ethyl α(β′-ethoxyethyl)propylmalonate* which on hydrolysis gave crystalline *α(β′-ethoxyethyl)propylmalonic acid*; this decarboxylated on heating to give *α(β′-ethoxyethyl)valeric acid*. The acid was converted into the acid chloride with the intention of obtaining the aldehyde by the method of Sonn and Muller (*Ber.*, 1919, **52**, 1927) but the acid chloride was found to rearrange spontaneously to give ethyl α(β′-chlorethyl)valerate.

Both these methods were repeated using β-phenoxyethyl bromide in place of β-ethoxyethyl bromide. *Ethyl α(β′-phenoxyethyl)propylcyanoacetate* hydrolysed and decarboxylated gave *α(β′-phenoxyethyl)valeronitrile* which was converted by Stephen's method to α(β′-phenoxyethyl)valeraldehyde in fair yield. The aldehyde was identified as crystalline 2 : 4-*dinitrophenylhydrazone*. Better yields were obtained starting from *ethyl α(β′-phenoxyethyl)propylmalonate*. This compound was hydrolysed to *α(β′-phenoxyethyl)propylmalonic acid* and on decarboxylation gave *α(β′-phenoxyethyl)valeric acid*. The acid was converted to the corresponding *anilide* and, by the application of the method of Sonn and Muller (*loc. cit.*), to α(β′-phenoxyethyl)valeraldehyde. This aldehyde condensed with 6-methoxy-4-quinolyl methyl ketone, but the product could not in spite of repeated attempts be obtained analytically pure. The aldehyde was eventually utilised (Work, unpublished) for the synthesis of 4-propylpiperidine and ethyl 4-propylpiperidine-2-carboxylate.

For the synthesis of 5-bromo-1-nitro-3-propylpentane (V), α(β′-phenoxyethyl)valeric acid was used as starting material. The acid was converted into the acid chloride (XI) and allowed to react with diazomethane to give *phenyl 3-diazoacetohexyl ether* (XII) in nearly quantitative yield. The diazoketone rearranged quantitatively by the Arndt–Eistert process to give ethyl β(β′-phenoxyethyl)hexoate (XIII). This ester reduced by the method of Bouveault and Blanc gave a good yield of *γ(β′-phenoxyethyl)hexyl alcohol* (XIV). The acetate of this alcohol heated with hydrobromic acid and acetic acid gave 1 : 5-*dibromo-3-propylpentane* (XV). Treatment of this dibromide with silver nitrite gave 5-bromo-1-nitro-3-propylpentane (V).



5-Bromo-1-nitro-3-propylpentane condensed readily with 6-methoxyquinoline-4-aldehyde by the method worked out in Part I (*loc. cit.*) but the nitrocarbinol (VI) could not be crystallised; it was reduced catalytically without purification, cyclisation taking place spontaneously. As might be expected owing to the possible formation of 4 racemates, the product was difficult to purify, but eventually a pure *hydrobromide* of dihydro-*x*-niquidine (VII) was obtained in small yield. There was obviously at least one other isomeride present but it could not be obtained in a pure state. *Dihydro-x-niquidine monohydrate* was obtained crystalline from the hydrobromide.

The synthetic material was tested biologically by Miss Ann Bishop, D.Sc., of the Molteno Institute, Cambridge, who reported that it was at least as active as quinine against *Plasmodium relictum* in canaries and about half as toxic.

Experimental.

Ethyl α(β′-Ethoxyethyl)propylcyanoacetate.—To sodium ethoxide (5·3 g. Na) in dry alcohol was added ethyl propylcyanoacetate (36·6 g.). β-Bromoethyl ether (36·5 g.) was added to the boiling mixture during 15 minutes. After five hours the alcohol was allowed to distil slowly until no more came over. The residual oil was diluted with water and the product collected. The *ester* was purified by repeated fractional distillation at reduced pressure and the fraction, b. p. 157—161°/19 mm., was finally collected (Found: C, 63·5; H, 9·1. $C_{12}H_{21}O_3N$ requires C, 63·4; H, 9·3%).

α(β′-Ethoxyethyl)propylcyanoacetic Acid.—Ethyl ethoxyethylpropylcyanoacetate (15 g.) was hydrolysed by heating on a steam-bath with aqueous alcoholic potassium hydroxide (1 part 50% KOH, 4 parts alcohol) for 4 hours. The alcohol was removed and the ethoxyethylpropylcyanoacetic acid liberated by cautious addition of sulphuric acid to the cooled sodium salt. The *product* was purified by distillation and the fraction, b. p. 154—155°/0·2 mm. (10·8 g.), collected (Found: C, 60·9; H, 8·7. $C_{10}H_{17}O_3N$ requires C, 60·3; H, 8·5%).

α(β′-Ethoxyethyl)valeronitrile.—The cyanoacetic acid (10·5 g.) was decarboxylated by distilling slowly at 750 mm. The fraction, b. p. 214—220°, was redistilled when practically the whole (5·73 g.) distilled between 214° and 216° (Found: C, 70·0; H, 10·9. $C_9H_{17}ON$ requires C, 69·7; H, 11·0%).

α(β′-Ethoxyethyl)valeraldehyde.—Ethoxyethylvaleronitrile (10 g.) was added to a solution of dry stannous chloride (30 g.) in ether saturated with dry hydrogen chloride. The mixture was shaken overnight and then refluxed gently for seven hours. The heavy oil which settled at the bottom was washed thrice with ether by decantation and then dissolved in 3N-HCl. The acid solution was extracted with ether and the ether extract dried. The residual oil (3·6 g.) after removal of ether was distilled and the fraction, b. p. 180—220°/760 mm. (2 g.), was collected. This gave a crystalline 2 : 4-*dinitrophenylhydrazone*, m. p. 88° (Found: C, 52·6; H, 6·3; N, 17·2. $C_{15}H_{22}O_5N_4$ requires C, 53·2; H, 6·5; N, 16·6%).

Ethyl α(β′-Ethoxyethyl)propylmalonate.—To a mixture of diethyl propylmalonate (82·5 g.) and sodium ethoxide (9·2 g. Na) β-bromoethyl ether (60·7 g.) was added slowly enough to avoid an uncontrollable reaction. The mixture was boiled until neutral to litmus, excess of alcohol removed under reduced pressure, and the product diluted with water. The oil which separated was fractionally distilled and the *compound*, b. p. 158—162°/17 mm. (48 g.), collected (Found: C, 61·2; H, 9·3. $C_{14}H_{26}O_5$ requires C, 61·3; H, 9·5%).

α(β′-Ethoxyethyl)propylmalonic Acid.—The ester (48 g.) was hydrolysed by boiling aqueous potassium hydroxide

The *acid* (36·9 g.), m. p. 104—105°, liberated by careful acidification, crystallised from ether–ligroin (Found: C, 54·9; H, 8·1. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%).

α(β'-Ethoxyethyl)valeric Acid.—The substituted malonic acid (35 g.) decarboxylated and distilled in the usual way gave *α(β'-ethoxyethyl)valeric acid* (23·5 g.), b. p. 132—134°/4 mm. (Found: C, 61·8; H, 10·3. $C_9H_{18}O_3$ requires C, 62·1; H, 10·3%).

Ethyl α(β'-Chloroethyl)valerate.—With the intention of preparing the acid chloride from ethoxyethylvaleric acid this acid in dry chloroform was treated with thionyl chloride. The product was distilled and an 84% yield obtained of an oil, b. p. 170°/165 mm. This oil was found to have the reactions of an ester and to contain an unreactive halogen. There appeared to have been interchange of the Cl and OEt groups (Found: C, 56·3; H, 8·9. Calc. for $C_9H_{17}O_2Cl$: C, 56·1; H, 8·8%).

Ethyl α(β'-Phenoxyethyl)propylcyanoacetate.—To a boiling solution of ethyl propylcyanoacetate (62 g.) in alcoholic sodium ethoxide (8·6 g. Na) phenoxyethyl bromide (75 g.) was added at such a rate that the reaction did not get out of hand. Heating was continued for a further 45 minutes. The *product* (58·3 g.) isolated in the usual way had b. p. 155—158°/1·5 mm. (Found: C, 69·4; H, 7·5. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·6%).

α(β'-Phenoxyethyl)valeronitrile.—The cyanoacetic ester was hydrolysed and decarboxylated in the same way as the corresponding ethoxyethylcyanoacetic ester. The *product* distilled at 200°/18 mm. (Found: C, 76·8; H, 8·5. $C_{13}H_{17}ON$ requires C, 76·8; H, 8·4%). The intermediate *phenoxyethylcyanoacetic acid*, crystallised from benzene, had m. p. 112° (Found: C, 68·4; H, 7·0. $C_{14}H_{17}O_3N$ requires C, 68·0; H, 6·9%).

α(β'-Phenoxyethyl)valeraldehyde.—Phenoxyethylvaleronitrile (30 g.) was added to an ethereal solution of dry stannous chloride previously saturated with dry hydrogen chloride and the mixture shaken for 12 hours, boiled gently for 1 hour, and re-saturated with dry hydrogen chloride. This process was repeated and finally the ether was separated from the heavy oil. The oil was shaken with dilute hydrochloric acid and the ether soluble fraction extracted. It was found advantageous to add a small quantity of copper bronze to the extracted oil (13·8 g.) to prevent polymerisation; the oil could then be distilled under reduced pressure and the fraction, b. p. 186—189°/18 mm. (11·5 g.), collected. The aldehyde was identified by conversion to the 2 : 4-*dinitrophenylhydrazone*, which crystallised from ethanol as needles, m. p. 86° (Found: C, 58·8; H, 5·6; N, 14·3. $C_{19}H_{22}O_5N_4$ requires C, 59·1; H, 5·7; N, 14·5%).

Ethyl α(β'-Phenoxyethyl)propylmalonate.—Slow addition of phenoxyethyl bromide (280 g.) to a hot solution of diethyl propylmalonate (280 g.) in alcoholic sodium ethoxide (32 g. Na) followed by boiling of the resultant mixture for five hours gave after separation and fractional distillation in the usual way an *oil* (219 g.), b. p. 228—230°/18 mm. (Found: C, 67·6; H, 7·9. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·1%).

α(β'-Phenoxyethyl)propylmalonic Acid.—The ester from the above preparation (219 g.) was refluxed with aqueous alcohol and potassium hydroxide (150 g. KOH; 150 c.c. H_2O; 450 c.c. alcohol) for 1½ hours. The alcohol was removed under reduced pressure and the acid liberated from its sodium salt by slow addition of acid to a well cooled solution. The *acid* crystallised from ligroin–benzene as needles, m. p. 135° (Found: C, 63·3; H, 6·8. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%).

α(β'-Phenoxyethyl)valeric Acid.—Phenoxyethylpropylmalonic acid decarboxylated on warming above its m. p. The product distilled at 124°/20 mm. and solidified on standing. Crystallisation from light petroleum gave the *compound* as needles, m. p. 61° (Found: C, 70·2; H, 7·8. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%).

α(β'-Phenoxyethyl)valeranilide.—To phenoxyethylvaleric acid (107 g.) in benzene (135 c.c.) was added thionyl chloride (80·7 g.). The mixture was warmed for 30 minutes on a steam-bath and then solvent and excess thionyl chloride were removed under reduced pressure. The residual oil was mixed with benzene (270 c.c.) and added slowly to a mixture of aniline (107·5 g.) in benzene (270 c.c.) cooled in ice. After 1 hour the solution was washed free from aniline hydrochloride and the solvent removed. The product crystallised when triturated with ligroin and was recrystallised from a mixture of ligroin (500 c.c.) and benzene (10 c.c.). The *anilide* (124 g.), needles, had m. p. 103° (Found: C, 76·6; H, 7·6. $C_{19}H_{23}O_2N$ requires C, 76·8; H, 7·7%).

To phenoxyethylvaleranilide (50 g.) in benzene (100 c.c.) phosphorus pentachloride (42 g.) was added in small lots. When the vigorous reaction had subsided, benzene and phosphorus oxychloride were removed under reduced pressure. The residue was mixed with a solution of dry stannous chloride (140 g.) in dry ethereal hydrochloric acid (1000 c.c.). After shaking for 12 hours the mixture was boiled gently under reflux for 8 hours. The ether was decanted from the heavy oil which was dissolved in 2N-HCl (500 c.c.). Copper bronze (1 g.) and light petroleum (400 c.c.) were added to the acid solution and the whole shaken vigorously until on standing only two layers of liquid formed. The light petroleum was separated, washed, and dried. Before removing the solvent, fresh copper bronze was added to prevent polymerisation of the aldehyde (23 g.) which gave a 2 : 4-dinitrophenylhydrazone identical with that obtained from phenoxyethylvaleraldehyde prepared from the nitrile (see above).

Phenyl 3-Diazoacetohexyl Ether.—Phenoxyethylvaleric acid (46 g.) was converted into the acid chloride by treatment with thionyl chloride (1·25 mols.) in benzene. Excess of thionyl chloride was removed under reduced pressure and the acid chloride, dissolved in ether, was added to an ice cold ethereal solution of diazomethane (82 g. nitrosomethylurea). After twelve hours at room temperature most of the ether was removed under reduced pressure without raising the temperature. The *diazoketone* crystallised as pale yellow needles (44 g.), m. p. 50—51° (Found: C, 67·9; H, 7·2. $C_{14}H_{18}O_2N_2$ requires C, 68·3; H, 7·3%).

Ethyl β(β'-Phenoxyethyl)hexoate.—The diazoketone (44 g.) was rearranged by adding freshly prepared silver oxide (5 g.) in small lots to its alcoholic solution warmed to 60°. After removal of solvent and silver the *product* (40·3 g.) distilled at 188—192°/14 mm. (Found: C, 73·1; H, 9·1. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·1%).

γ(β'-Phenoxyethyl)hexyl Alcohol.—The ester from the above preparation (30 g.) reduced with sodium (17·6 g.) in alcohol (140 c.c.) gave after fractional distillation of the product an *oil* (22·7 g.), b. p. 190°/14 mm. (Found: C, 75·9; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). The alcohol gave a crystalline 3 : 5-*dinitrobenzoate*, m. p. 71°, needles from methanol (Found: C, 60·7; H, 5·9. $C_{21}H_{24}O_7N_2$ requires C, 60·6; N, 5·8%).

γ(β'-Phenoxyethyl)hexyl Acetate.—A mixture of phenoxyethylhexyl alcohol (66·6 g.) and pyridine (60 c.c.) was cooled in ice and acetyl chloride (24 g.) added slowly. The reaction was completed by warming the mixture for 5 minutes on the steam-bath. The product was poured into water, and the *oil* which separated was washed with acid and alkali, dried, and fractionally distilled, the portion (72·4 g.), b. p. 191—193°/14 mm., being collected (Found: C, 73·0; H, 9·2. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·1%).

1 : 5-*Dibromo-3-propylpentane.*—Glacial acetic acid saturated at room temperature with dry hydrobromic acid (39 c.c.) and phenoxyethylhexyl acetate (15 g.) were heated together in a sealed tube at 100° for 9 hours and then at 145° for another 9 hours. The product was poured into water and extracted with ether. The ether was washed with alkali and the *product* distilled. The fraction (12·2 g.), b. p. 132—136°/16 mm., was collected (Found: Br, 58·0. $C_8H_{16}Br_2$ requires Br, 58·8%).

5-Bromo-1-nitro-3-propylpentane.—To dibromo*iso*octane (40 g.) in a flask fitted with a high speed stirrer and a nitrogen inlet freshly prepared silver nitrite (32 g.) was added in small lots during 6 hours. Nitrogen was bubbled slowly through the stirred solution for a further 36 hours. Silver bromide was removed and the *product* fractionally distilled. The

fraction, b. p. 104—108°/0·8 mm. (16 g.), was collected (Found: C, 40·3; H, 6·9; N, 6·1. $C_8H_{16}O_2NBr$ requires C, 40·3; H, 6·7; N, 5·9%).

Dihydro-x-niquidine.—To a suspension of the bisulphite compound of 6-methoxyquinoline-4-aldehyde (8·5 g.) in water (100 c.c.) warmed to 40° was added an ice-cold mixture of bromonitro*iso*octane (6·2 g.) and sodium methoxide (1·5 g. Na) in methyl alcohol (20 c.c.). The reactants were shaken vigorously for two minutes and then after another five minutes the supernatant liquid was decanted from the heavy gum which had separated. All efforts to crystallise this product failed. The gum was dissolved in methanol and hydrogenated in the presence of hydrogen and excess of carbon dioxide at room temperature and 5 atmospheres pressure using Raney nickel catalyst. After shaking for four hours the catalyst was removed and the product concentrated. When most of the alcohol had been removed acetone was added and after several hours the crystalline product (1·5 g.) was collected. This material appeared to contain more than one crystalline hydrobromide, but only one compound (0·4 g.) was obtained pure, m. p. 230—231°, after repeated fractional crystallisation from water and from methyl alcohol–acetone. Analytical results showed this to be the *monohydrobromide* of dihydro-*x*-niquidine (Found: C, 58·3; H, 6·9; N, 6·9. $C_{19}H_{26}O_2N_2,HBr$ requires C, 57·7; H, 6·8; N, 7·1%). The base isolated from the hydrobromide was obtained crystalline as a *monohydrate*, m. p. 98—100°, from aqueous acetone (Found: C, 68·5; H, 8·5. $C_{19}H_{26}O_2N_2,H_2O$ requires C, 68·6; H, 8·4%).

National Institute for Medical Research, London, N.W.3. [*Received, December 5th*, 1945.]

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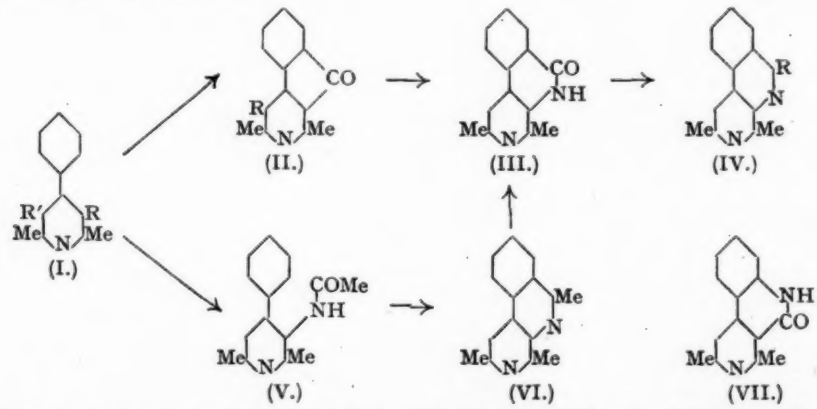
53. *New Syntheses of Heterocyclic Compounds. Part V. The Schmidt Rearrangement of* 1 : 3-*Dimethyl-2-azafluorenone.*

By Vladimir A. Petrow.

With the object of preparing naphthyridine derivatives suitable for biological examination, 1 : 3-dimethyl-2-azafluorenone (II; R = H) has been submitted to the Schmidt reaction and a *substance*, $C_{14}H_{12}ON_2$, obtained in yields approaching 90%. This compound may be represented by either (III) or (VII). Its formulation as a 9-*hydroxy*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene* (2-*hydroxy*-3 : 4-*benz*-6 : 8-*dimethyl*-1 : 7-*naphthyridine*) (III) followed from the observation that the same compound was obtained by oxidation of 1 : 3 : 9-*trimethyl*-2 : 10-*diazaphenanthrene* (VI) with chromic acid. 9-Hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene has been converted into the *chloro*-derivative (IV; R = Cl) and hence into the *amino*-, *piperidino*- and *phenoxy*-derivatives.

The object of the present investigation was to study the ring enlargement of 1 : 3-dimethyl-2-azafluorenone (II; R = H) by the Beckmann and Schmidt rearrangements so as to obtain a hydroxydimethyldiazaphenanthrene (hydroxybenzdimethylnaphthyridine). This was required as part of a wider programme dealing with the relation between chemical constitution and biological action in the naphthyridine series. Such ring systems involving two adjacent pyridine nuclei may well be expected to possess some degree of biological interest. It was therefore not surprising that certain members of the group, prepared in these laboratories, have shown outstanding properties on preliminary examination. The biological results, on completion, will be referred to in a subsequent communication.



The Beckmann rearrangement of fluorenone oxime to phenanthridone was first described by Beckmann and Wegerhoff (*Annalen*, 1889, **252**, 39; cf. Pictet, *Chem. Zeit.*, 1894, **18**, 1822; Kerp, *Ber.*, 1896, **29**, 230). The yield was very low, but was subsequently increased to 30% by Pictet and Gonset (*Arch. Sci. phys. nat.*, 1897, **3**, 3751). Moore and Huntress (*J. Amer. Chem. Soc.*, 1927, **49**, 2618), by carrying out the rearrangement with phosphorus pentachloride in phosphorus oxychloride, still further improved the yield, preparing 7-nitrophenanthridone from 2-nitrofluorenone oxime. Attempts to apply this reaction to the oxime of 1 : 3-dimethyl-2-azafluorenone (Borsche and Hahn, *Annalen*, 1939, **537**, 229) under a variety of experimental conditions were uniformly unsuccessful. Extensive resinification occurred or the starting materials were recovered unchanged. This result may be related to the stereochemical configuration of the oxime since Jeiteles (*Monatsh.*, 1896, **17**, 515) has shown that only one of the two oximes of phenyl 3-pyridyl ketone undergoes a Beckmann rearrangement to give a product hydrolysed to nicotinic acid and aniline [cf. (II; R = H) → (III) described below].

Attention was therefore directed to the Schmidt reaction (*Ber.*, 1924, **57**, 704; 1925, **58**, 2413) whereby cyclic ketones suffer ring enlargement when treated with hydrazoic acid in the presence of a suitable catalyst. This reaction forms the basis for the synthesis of phenanthridones from fluorenones described in B.P. 333,173. It has been further improved and its scope considerably extended by Walls (*J.*, 1935, 1405) who modified the experimental conditions, replacing a benzene solution of hydrazoic acid by a concentrated aqueous solution of the commercially available sodium azide, which was added to a cooled solution of the ketone in concentrated sulphuric acid.

When 1 : 3-dimethyl-2-azafluorenone (Mills, Palmer, and Tomkinson, *J.*, 1924, 2365) (II; R = H) was submitted to the Schmidt reaction, a homogeneous *hydroxydimethyldiazaphenanthrene* was readily obtained in yields approaching 90%. The rearrangement of the unsymmetrical fluorenone (II; R = H) may give rise to either a 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene (III) or to a 9-hydroxy-6 : 8-dimethyl-7 : 10-diazaphenanthrene (VII).* A decision in favour of the former alternative was made possible by a study of the oxidation of 1 : 3 : 9-*trimethyl*-2 : 10-*diazaphenanthrene* (VI), which was obtained fairly readily by the following series of reactions: 4-Phenyl-lutidine dicarboxylic ester (I; R = R′ = CO_2Et) gave a monoester on partial hydrolysis (Hantzsch, *Ber.*, 1884, **17**, 2910) from which 4-phenyl-lutidine-3-carboxylic ester (I; R = CO_2Et, R′ = H) was obtained by distillation at atmospheric pressure. Conversion of this ester to the acid chloride (Borsche and Hahn, *ibid.*, p. 228) followed by treatment with aqueous ammonia gave the *amide*, smoothly converted by hypobromite into 3-*amino*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NH_2, R′ = H). The *acetyl derivative* (V) of this amine failed to undergo ring closure with such condensing agents as anhydrous zinc chloride or phosphorus oxychloride. Fusion with phosphorus pentoxide at 270° (cf. Petrow, Stack, and Wragg, *J.*, 1943, 316) gave 1 : 3 : 9-trimethyl-2 : 10-diazaphenanthrene (VI) in *ca.* 10% yield; but, when the acetyl derivative (V) was heated with phosphorus pentoxide in ψ-cumene the yield of (VI) rose to 30%. 3-*Benzamido*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NHBz, R′ = H) similarly gave 9-*phenyl*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene* (IV; R = Ph).

Walls (*J.*, 1935, 1405) has shown that oxidation of 9-methylphenanthridines with chromic acid leads to the formation of the corresponding phenanthridones in nearly quantitative yield, and it was therefore expected that (VI), which bears a formal analogy to 9-methylphenanthridine, would behave in a similar way. Oxidation of 1 : 3 : 9-trimethyl-2 : 10-diazaphenanthrene (VI) with chromic acid gave a complex mixture of products from which 9-*hydroxy*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene* (III) was readily isolated owing to its low solubility in alcohol. This compound proved to be identical in m. p. and mixed m. p. with the rearrangement product of 1 : 3-dimethyl-2-azafluorenone with hydrazoic acid, to which must therefore be assigned the formulation (III).

A parallel series of experiments were also carried out with the object of preparing 4-amino-1 : 3-dimethyl-2-azafluorenone (II; R = NH_2). This compound was required for alkaline fusion when, in analogy with the quantitative conversion of 4-aminofluorenone into phenanthridone (Graebe and Schestakow, *Annalen*, 1895, **284**, 312) it was hoped to obtain a compound represented by formula (III). 4-Phenyl-lutidinedicarboxylic acid monoethyl ester (I; R = CO_2H, R′ = CO_2Et) (Hantzsch, *loc. cit.*) was converted into the *ester-amide via* the acid chloride and hence, by hypobromite treatment, into 3-*amino*-5-*carbethoxy*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NH_2, R′ = CO_2Et). Hydrolysis followed by acetylation gave the *diacetyl derivative* of the corresponding *acid* (I; R = NAc_2, R′ = CO_2H). Attempts to convert this compound into (II; R = NH_2) by ring closure with sulphuric acid were unsuccessful. This failure may have been due to the facile hydrolysis of the diacetyl group. As it was hoped that the benzamido group might prove more resistant to hydrolysis, 3-*benzamido*-5-*carbethoxy*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NHBz, R′ = CO_2H) was prepared by hydrolysis of the corresponding *ester* (I; R = NHBz, R′ = CO_2Et). On submitting this compound to ring closure experiments, the initial action again appeared to be hydrolysis of the benzamido group and further experiments in this direction were abandoned.

Treatment of 9-hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene (III) with phosphorus pentachloride in phosphorus oxychloride suspension in a sealed tube at 180° led to the formation of the corresponding *chloro-compound* (IV; R = Cl), from which the *phenoxy-*, *amino-*, and *piperidino-derivatives* were obtained. Reduction of (IV; R = Cl) with red phosphorus and hydriodic acid in a sealed tube was not successful, the hydroxy compound (III) being regenerated unchanged. Hydrazoic acid was without action on a solution of (III) in concentrated sulphuric acid, there being no evidence for the formation of a tetrazole derivative (cf. ε-leucine lactam → pentamethylenetetrazole, Schmidt, *Ber.*, 1924, **57**, 706).

Experimental.

M. ps. are corrected.

9-*Hydroxy*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene* (III).—1 : 3-Dimethyl-2-azafluorenone (160 g.) (Mills, Palmer, and Tomkinson, *loc. cit.*) dissolved in concentrated sulphuric acid (1000 ml.) was treated at 0° whilst mechanically stirred with a solution of sodium azide (90 g.) in water (250 ml.), added dropwise over a period of 5 hours. After some hours the mixture was poured on ice (2500 g.). The precipitated sulphate was collected after 12 hours and the base regenerated by treatment with dilute ammonia on the water-bath. After extraction with spirit (1500 ml.) it (90%) is sufficiently pure for conversion into the chloro compound. 9-*Hydroxy*-1 : 3-*dimethyl*-2 : 10-*diazaphenanthrene* formed prismatic

* *Note on nomenclature.*—The nomenclature employed is based upon phenanthrene and not upon benznaphthyridine. Furthermore, the phenanthrene nucleus is so numbered that the substituent in the middle ring is always attached to C_9. This is necessary in order to simplify subsequent discussion on the relationship between structure and biological activity.

needles from nitrobenzene, m. p. 319—320° (Found: C, 75·0; H, 5·4; N, 12·5. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4; N, 12·5%). A saturated alcoholic solution gives a faint but distinct yellow colouration with ferric chloride solution. It is sparingly soluble in aqueous sodium hydroxide, but readily soluble in sodium ethoxide solution.

9-Chloro-1 : 3-dimethyl-2 : 10-diazaphenanthrene (IV; R = Cl).—The very finely powdered hydroxy compound (2·0 g.), phosphorus pentachloride (2·5 g.), and phosphorus oxychloride (15 ml.) were heated in a sealed tube at 180° for 4 hours. After 12 hours at room temperature the product was collected, decomposed with ice, thoroughly extracted with 2N-hydrochloric acid, and the base precipitated by addition of ammonium hydroxide. After extraction with chloroform, it (40%) was crystallised (charcoal) from ligroin. *9-Chloro-1 : 3-dimethyl-2 : 10-diazaphenanthrene* formed needles, m. p. 153—154° (Found: Cl, 14·4. $C_{14}H_{11}N_2Cl$ requires Cl, 14·6%).

9-Phenoxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene (IV; R = OPh).—The chloro compound (1·2 g.) in phenol (5 g.) was heated at 180° for 5 hours. The product was digested with excess sodium hydroxide solution and the insoluble fraction isolated with chloroform. The product was extracted twice with ligroin (20 ml. each portion, b. p. 100—120°). The cooled extracts were decanted from some resinous material, the solvent removed and the residue, in alcohol, treated with picric acid. *9-Phenoxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene picrate* (1·75 g.) formed bright yellow plates from spirit, m. p. 203—203·5° (Found: N, 13·1. $C_{20}H_{16}ON_2,C_6H_3O_7N_3$ requires N, 13·2%). The *base*, regenerated by shaking the picrate with 10% sodium hydroxide solution, formed needles, m. p. 112—113° from ligroin (Found: C, 80·2; H, 5·4; N, 8·8. $C_{20}H_{16}ON_2$ requires C, 80·0; H, 5·3; N, 9·3%).

9-Amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene (IV; R = NH_2).—The chloro compound (2·7 g.) with saturated alcoholic ammonia (15 ml.) was heated in a sealed tube at 180—190° for 16 hours. The product was taken to dryness, extracted with water (charcoal) and the filtrate made alkaline with sodium hydroxide. The precipitated base was purified by means of the *picrate*, silky yellow needles, m. p. 261—262° (decomp.), from alcohol (Found: N, 18·6. $C_{14}H_{13}N_3,C_6H_3O_7N_3$ requires N, 18·6%). *9-Amino-1 : 3-dimethyl-2 : 10-diazaphenanthrene* formed cubic crystals, m. p. 189·5—190·5°, from ligroin containing a trace of alcohol (Found: C, 75·3; H, 5·9; N, 18·9. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·8; N, 18·8%). The *dihydrochloride* (60%) formed octahedra from aqueous alcoholic hydrogen chloride, m. p. >310° (Found: Cl, 22·7. $C_{14}H_{13}N_3,2HCl,H_2O$ requires Cl, 22·6%).

9-Piperidino-1 : 3-dimethyl-2 : 10-diazaphenanthrene (IV; R = NC_5H_{10}).—The chloro compound (1·5 g.) and piperidine (9 ml.) were heated in a sealed tube at 180° for 5 hours. The product was taken to dryness on the water-bath, stirred with a few drops of sodium hydroxide solution, and the free base extracted with chloroform and treated, in alcoholic solution, with picric acid. *9-Piperidino-1 : 3-dimethyl-2 : 10-diazaphenanthrene picrate* formed yellow plates, m. p. 228—229°, from alcohol (Found: N, 16·2. $C_{19}H_{21}N_3,C_6H_3O_7N_3$ requires N, 16·1%). The *base*, regenerated from the picrate with sodium hydroxide solution, formed octahedra, m. p. 113·5—114·5°, from aqueous methanol (Found: C, 78·2; H, 7·5; N, 14·3. $C_{19}H_{21}N_3$ requires C, 78·3; H, 7·2; N, 14·4%). The *dihydrochloride* separated from alcoholic hydrogen chloride in small needles, m. p. 165—166° (Found: Cl, 18·9. $C_{19}H_{21}N_3,2HCl$ requires Cl, 19·5%).

4-Phenyl-2 : 6-dimethylpyridine-3-carboxyamide (I; R = $CONH_2$, R′ = H).—The corresponding crude acid chloride (27 g., Borsche and Hahn, *loc. cit.*) in warm benzene (50 ml.) was added dropwise to ammonia (150 ml., *d*, 0·880) whilst mechanically stirred and cooled below 10°. After some hours, the product (23 g.) was collected and crystallised from acetone. *4-Phenyl-2 : 6-dimethylpyridine-3-carboxyamide* formed plates, m. p. 198—199° (Found: C, 74·3; H, 6·2; N, 12·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

3-Amino-4-phenyl-2 : 6-dimethylpyridine (I; R = NH_2, R′ = H).—The crude amide (90 g.), finely powdered, was added at 0° to a mechanically stirred solution of bromine (67·5 g.) in potassium hydroxide (1125 ml., 10%). After one hour, potassium hydroxide (675 ml. of 10%) was added to the clear solution and the mixture heated for 1½ hours on the water-bath. The base (51 g.) was isolated with benzene (500 ml.) (charcoal). *3-Amino-4-phenyl-2 : 6-dimethylpyridine* formed squat needles, m. p. 87—87·5°, from ligroin (Found: C, 78·8; H, 7·1; N, 14·3. $C_{13}H_{14}N_2$ requires C, 78·8; H, 7·1; N, 14·1%).

3-Acetamido-4-phenyl-2 : 6-dimethylpyridine (V).—The amino compound (20 g.), dry pyridine (60 ml.) and acetic anhydride (20 g.) were heated under reflux for 30 minutes. The product was made alkaline with ammonia, transferred to an evaporating basin and taken to dryness on the water-bath. The residue (almost quantitative) was crystallised (charcoal) either from aqueous acetone or from benzene–ligroin. *3-Acetamido-4-phenyl-2 : 6-dimethylpyridine* formed flat needles containing solvent of crystallisation, m. p. 162—163° (Found: C, 75·0; H, 6·7; N, 11·5. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%).

1 : 3 : 9-Trimethyl-2 : 10-diazaphenanthrene (VI).—3-Acetamido-4-phenyl-2 : 6-dimethylpyridine (10 g.) dissolved in dry technical ψ-cumene (30 ml.) in a 250 ml. flask was treated with phosphorus pentoxide (30 g.), and the mass rapidly mixed with a glass rod until fairly homogeneous. The mixture was heated under reflux (calcium chloride tube) at 200—210° for 8 hours. The product was decomposed with water, the base precipitated with ammonia, dissolved in spirit and treated with alcoholic picric acid. The picrate, m. p. 242—243° (decomp.), was crystallised once from a very large volume of spirit and the base regenerated with 10% sodium hydroxide solution. *1 : 3 : 9-Trimethyl-2 : 10-diazaphenanthrene* formed long faintly yellow glittering needles, m. p. 132·5—133°, from ligroin (Found: C, 80·8; H, 6·2; N, 12·4. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3; N, 12·6%). The *hydrochloride* separated from spirit in small crystals, m. p. >310° (Found for air-dried product: Cl, 12·6. $C_{15}H_{14}N_2,HCl,H_2O$ requires Cl, 12·8%).

9-Hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene (III).—1 : 3 : 9-Trimethyl-2 : 10-diazaphenanthrene (1·8 g.), glacial acetic acid (12 ml.), 2N-sulphuric acid (12 ml.), and finely powdered potassium dichromate (4·5 g.) were heated under reflux for 6 hours. The product was poured into excess ammonium hydroxide and the insoluble material collected and crystallised (200 mg.) three times from spirit. *9-Hydroxy-1 : 3-dimethyl-2 : 10-diazaphenanthrene* formed silky colourless needles, m. p. 320—321° (Found: C, 74·8; H, 5·3; N, 12·4. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4; N, 12·5%), not depressed in admixture with a sample prepared by the rearrangement of 1 : 3-dimethyl-2-azafluorenone with hydrazoic acid (above).

3-Benzamido-4-phenyl-2 : 6-dimethylpyridine, needles, m. p. 213—214°, from aqueous methyl alcohol (Found: C, 78·7; H, 6·0; N, 9·3. $C_{20}H_{18}ON_2$ requires C, 79·5; H, 6·0; N, 9·3%) was prepared by treating the base (900 mg.) in dry pyridine (2 ml.) with benzoyl chloride (700 mg.) for 1 hour on the water-bath.

9-Phenyl-1 : 3-dimethyl-2 : 10-diazaphenanthrene (IV; R = Ph).—Prepared by ring closure of 3-benzamido-4-phenyl-2 : 6-dimethylpyridine with phosphorus pentoxide in ψ-cumene (as above) separated (30%) with water of crystallisation as felted silky needles, m. p. 131—132°, from aqueous methanol (Found: C, 84·1; H, 5·5; N, 10·0. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·6; N, 9·9%). The *picrate* formed bright yellow needles, m. p. 206—207°, from alcohol (Found: N, 13·6. $C_{20}H_{16}N_2,C_6H_3O_7N_3$ requires N, 13·6%). The *monohydrochloride* separated from alcohol in stout needles, m. p. >300° (Found: Cl, 10·6. $C_{20}H_{16}N_2,HCl$ requires Cl, 10·8%).

5-Carbethoxy-4-phenyl-2 : 6-dimethylpyridine-3-carboxyamide (I; R = $CONH_2$; R′ = CO_2Et).—The corresponding acid-ester (30 g.) (Hantzsch, *loc. cit.*) was gently refluxed with thionyl chloride (100 ml.) for 30 minutes. The product was taken to dryness under reduced pressure on the water-bath and the residual oil, dissolved in benzene (50 ml.), added dropwise to mechanically stirred ammonium hydroxide (150 ml., d, 0·880) cooled below 10°. After 24 hours at the ordinary temperature, the precipitated material was collected and purified from aqueous acetone. *5-Carbethoxy-4-*

phenyl-2 : 6-*dimethylpyridine*-3-*carboxyamide* (18 g.) formed flat needles, m. p. 180—181° (Found: C, 68·5; H, 6·0; N, 9·6. $C_{17}H_{18}O_3N_2$ requires C, 68·5; H, 6·0; N, 9·4%).

3-*Amino*-5-*carbethoxy*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NH_2, R′ = CO_2Et).—The finely powdered amide (26 g.) was added in one portion to a mechanically stirred ice-cold solution of bromine (15 g.) in potassium hydroxide (250 ml., 10%). After 45 minutes, a further volume of potassium hydroxide (150 ml., 10%) was added to the clear solution. The mixture was heated on the water-bath for 30 minutes and the amide salted out by addition of sodium chloride (100 g.). After some hours at 0°, the crystalline product was collected. The *compound* (50%) formed needles, m. p. 124·5—125·5°, from ligroin (Found: C, 70·8; H, 6·5; N, 10·4. $C_{16}H_{18}O_2N_2$ requires C, 71·1; H, 6·7; N, 10·4%).

3-*Diacetylamino*-5-*carboxy*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NAc_2, R′ = CO_2H).—The above amino-ester (10 g.), potassium hydroxide (6·8 g.), and absolute alcohol (22 ml.) were heated under reflux for 3 hours on the water-bath. The mixture was diluted to *ca.* 250 ml. with absolute alcohol and carbon dioxide passed in until precipitation was complete. The filtrate was taken to dryness on the water-bath and the crystalline residue heated under reflux with acetic anhydride (100 ml.) for 1 hour. The product was taken to dryness on the water-bath under reduced pressure and the residue crystallised from alcohol. 3-*Diacetylamino*-5-*carboxy*-4-*phenyl*-2 : 6-*dimethylpyridine* formed octahedra, m. p. 240—241° (Found: C, 66·4; H, 5·5; N, 8·6. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5; N, 8·6%).

3-*Benzamido*-5-*carbethoxy*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NHBz, R′ = CO_2Et).—Crude 3-amino-5-carbethoxy-4-phenyl-2 : 6-dimethylpyridine (58 g.) dissolved in dry pyridine (200 ml.) was treated with benzoyl chloride (30 g.) with cooling. Reaction was completed by heating for 30 minutes on the water-bath. 3-*Benzamido*-5-*carbethoxy*-4-*phenyl*-2 : 6-*dimethylpyridine*, glittering needles (66%) from aqueous methyl alcohol, separated in dimorphic forms having melting points of 156—157° and 170—171° (Found: C, 73·7; H, 6·1; N, 7·4. $C_{23}H_{22}O_3N_2$ requires C, 73·8; H, 5·9; N, 7·5%).

3-*Benzamido*-5-*carboxy*-4-*phenyl*-2 : 6-*dimethylpyridine* (I; R = NHBz, R′ = CO_2H).—The corresponding ester (52·3 g.), potassium hydroxide (8·5 g.), and absolute alcohol (100 ml.) were heated under reflux for 80 hours. The alcohol was removed on the water-bath and the product extracted several times with small quantities of water (28 g. unchanged material recovered). The extracts and washings were acidified with sulphuric acid (8·5 g.) diluted with a little water, and the precipitated acid (19 g.) crystallised from alcohol–light petroleum. The *compound* formed stout needles, m. p. 276—277° (decomp.) (Found: C, 72·8; H, 5·2; N, 8·2. $C_{21}H_{18}O_3N_2$ requires C, 72·8; H, 5·2; N, 8·1%).

The author thanks the Therapeutic Research Corporation of Great Britain Limited for generous grants, and for certain facilities. The laboratory accommodation, kindly placed at the disposal of Queen Mary College by the University of Cambridge, is gratefully acknowledged.

QUEEN MARY COLLEGE (UNIVERSITY OF LONDON), E. 1. [*Received, November 8th*, 1945.]

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54. *The Persulphate–Iodide Reaction. Part III. Specific Effects of Univalent and Bivalent Cations. The Activation Energy of the Reaction.*

By W. J. HOWELLS.

The gradients of the log k–$\sqrt{I}$ curves for the reaction in solutions containing corresponding chlorides and sulphates are compared and are found to be higher for the chloride solutions. A comparison is made between the salt effects of cations in relation to their size and valency. These effects decrease in the sequence $K^{\cdot} > Zn^{\cdot\cdot} > Mg^{\cdot\cdot} > Be^{\cdot\cdot} > Na^{\cdot} > Li^{\cdot} > H^{\cdot}$. The activation energy of the reaction has been determined in the presence, separately, of chlorides of potassium, sodium, and hydrogen, and appears to increase in this sequence. The relation between the activation energy and the collision factor is discussed, and the relatively low values of both are considered.

RESULTS recorded in Part I (Howells, *J.*, 1939, 463) show that the velocity of the persulphate–iodide reaction varies with the nature of the cations present in the reaction solution. That there should be velocity variation in the presence of different ions is suggested by the extended Debye–Hückel equation given in Part I, *viz.*,

$$\ln k = \ln k_0 + 2\alpha Z_a Z_b \sqrt{I} + (\beta_1 + \beta_2 - \beta_x)I$$

where the β terms are specific terms partly dependent upon the nature of all the ions in the reaction solution.

When the cations were present, separately, in equivalent concentrations, it was found that the velocity constant decreased in the series $Cs^{\cdot} > Rb^{\cdot} > K^{\cdot} > NH_4^{\cdot} > Na^{\cdot} > Li^{\cdot} > H^{\cdot}$. The investigation has now been extended to include some bivalent cations, but calcium, strontium, and barium could not be included owing to the formation of sulphate ions.

A further object of the present work was to determine and compare the collision factors of the reaction in the presence, separately, of potassium, sodium, and hydrogen ions.

EXPERIMENTAL.

The general procedure has been described in Part I. The velocity constants were calculated from the bimolecular equation $k = x/at(a - x)$, a being the initial concentrations of persulphate and iodide in g.-equivs./l., and x the number of g.-equivs./l. of iodine liberated in t minutes. The iodine liberated was estimated by titration with 0·01N-sodium thiosulphate solution, the reaction being sufficiently arrested by dilution of 25 c.c. of the reaction mixture in 250 c.c. of distilled water. Starch solution was added towards the end of each titre. The experimental conditions brought about a premature end-point, and the blue colour returned; this was therefore discharged by a few additional drops of thiosulphate solution, and the titration considered completed. This procedure was consistently followed throughout.

The velocity of the persulphate–iodide reaction is increased slightly by light (von Kiss, *Rec. Trav. chim.*, 1927, **46**, 230; Soper and Williams, *Proc. Roy. Soc.*, 1933, *A*, **140**, 59), so the reaction vessel was only weakly illuminated by artificial light.

Specific Ion Effect.—The velocity constants for the reaction, at 25°, were determined in the presence, separately, of potassium, sodium, lithium, cadmium, zinc, magnesium, and beryllium sulphates. The reaction solutions contained

in each case 0·01666N-iodide and 0·01666N-persulphate, together with 0·005N-sulphuric acid. The lithium and beryllium sulphates used were the purest obtainable. All other materials used were "AnalaR," and these, with the exception of sodium and cadmium sulphates, were further purified by recrystallisation. The sulphates were, where necessary, dehydrated, and weighed in the anhydrous state.

Satisfactory bimolecular velocity constants were obtained, and these are recorded in Table II. Those for the reaction in the presence of chlorides were obtained by intrapolation, using data given in Part II (*J.*, 1941, 643). The velocity constants recorded for the sulphate solutions are mean values, and a detailed example is given in Table I(*a*).

TABLE I.

(*a*) 0·01666N-$K_2S_2O_8$ + 0·01666N-KI + 0·005N-H_2SO_4 + 0·1000M-$BeSO_4$; 25°.

t.	$x \times 10^5$.	$k \times 10^3$.	*t.*	$x \times 10^5$.	$k \times 10^3$.
37·4	214	237	77·3	384	232
49·1	270	237	85·4	415	233
63·3	330	234	93·2	446	235

$k \times 10^3$ (mean) = 235.

(*b*) 0·01666N-$K_2S_2O_8$ + 0·01666N-KI + 0·3500M-HCl; 15°.

t.	$x \times 10^5$.	$k \times 10^3$.	*t.*	$x \times 10^5$.	$k \times 10^3$.
40·6	137	132	105·0	302	126
62·1	197	130	120·3	335	125
85·5	256	128	126·4	346	125

$k \times 10^3$ (initial value) = 135.

DISCUSSIONS OF RESULTS.

Results recorded in Part I (*loc. cit.*) show that the velocity constant for the persulphate–iodide reaction, in the presence of different univalent cations, decreases in the series caesium to lithium, *i.e.*, with decreasing ionic radius. Table II shows that this is true also for the Group II cations involved, with the exception of that of cadmium. That the velocity rates are related to the radii of the ions present is to be expected, since the electric field within the reaction solution depends to some extent upon the radii of the ions present. The radii of zinc and magnesium ions do not differ much, and neither do the corresponding rates. The radius value given for the beryllium ion is considered doubtful.

The relatively low velocity in the cadmium sulphate solution is due to the fact that the cadmium forms complex ions with the iodide in the reaction solution, thus removing part of one of the reactants: $2CdI_2 \rightleftharpoons Cd(CdI_4) \rightleftharpoons Cd^{\cdot\cdot} + CdI_4''$. That this is so is indicated also by the lower velocity in 0·1000M- than in 0·0333M-cadmium sulphate solution, since an increase in ionic strength is usually accompanied by an increase in the rate of the reaction.

Table II, (*c*) and (*e*), shows that the rate of the reaction in the presence of 0·1M-potassium chloride exceeds the rate in the presence of 0·05M-potassium sulphate, although the total ionic strength of the reaction solution is considerably higher in the latter case. Both reaction solutions contain the same concentration of potassium ions. Similar observations apply to the reaction in the presence of 0·2M-potassium chloride and 0·1M-potassium sulphate, and to the reaction in the presence, separately, of equivalent concentrations of sodium chloride and sulphate.

It follows that the log k–$\sqrt{I}$ curves for the reaction have steeper gradients in solutions containing the chlorides than in those containing the corresponding sulphates. It is evident that the specific effects of the ions present, represented by the β terms in the extended Debye–Hückel equation, are of considerable significance in their bearing upon the reaction rate.

The gradients of the log k–$\sqrt{I}$ curves are, at the concentrations concerned, nearly the same for the solutions containing zinc, magnesium, sodium, and beryllium sulphates.

Table II, (*a*) and (*b*), records the rates of the reaction in the presence of equimolecular amounts of sulphates. It being borne in mind that the added concentration of univalent cations is double that of bivalent ones, a comparison may be made between the salt effects of the two types of cations. Excluding the case of potassium, the superior effect of the bivalent cations, with their double charge and more powerful electric fields, is apparent. The relatively low reaction rate in the cadmium sulphate solution is due to causes already stated.

The data for solutions containing 0·05M-potassium sulphate and 0·1M-zinc, magnesium, and beryllium sulphates, severally, Table II, (*b*) and (*e*), enable a comparison to be made between the salt effects due to the addition of equal concentrations of the cations involved. The largest salt effect is caused by the potassium ion, and this is due, probably, to the fact that its ionic radius is a dominating factor. A numerical example will illustrate this for the solutions concerned.

The Debye–Hückel equation, in its extended form, for the iodide–persulphate reaction in aqueous solutions, may be written: $\log k = \log k_0 + 2\sqrt{I} + \beta I$, since, in this case, $2\alpha Z_a Z_b / 2{\cdot}303 = 2$, approximately.

The value of k_0, the velocity constant at zero ionic strength, is taken as 0·06 (see Part I, *loc. cit.*). Using the appropriate values of k and I, it may be shown that the values of the β terms are −1·31, −1·61, −1·65, and −1·66, respectively, for the solutions containing potassium, zinc, magnesium, and beryllium ions. The β term is a composite one, but it, nevertheless, represents in part the contribution made by the cations present. The β values are negative since a gradient of 2 applies to the log k–$\sqrt{I}$ curve for this reaction only when the ionic strength is low.

In Table II, k = the observed velocity constant; I = the total ionic strength of the reaction solution concerned; F = an arbitrary kinetic activity factor = k/k_a, where k_a = 0·142, the velocity constant in the absence of neutral salt.

Activation Energies.—The activation energy of the reaction has been taken as equivalent to its critical increment, and an attempt has been made to ascertain whether it increases with ionic strength and whether

TABLE II.

0·01666N-$K_2S_2O_8$ + 0·01666N-KI + 0·005N-H_2SO_4 + neutral salt; 25°.

Concn. of neutral salt: (*a*) 0·0333M, (*b*) 0·1000M.

	Salt.	K_2SO_4.	Na_2SO_4.	Li_2SO_4.	$CdSO_4$.	$ZnSO_4$.	$MgSO_4$.	$BeSO_4$.
(*a*)	*k*	0·221	0·171	0·160	0·156	0·194	0·188	—
	I	0·1491	—	—	0·1824	—	—	—
(*b*)	*k*	0·347	0·223	—	0·148	0·248	0·239	0·235
	F	2·44	1·57	—	1·04	1·74	1·70	1·65
	I	0·3492	—	—	0·4492	—	—	—

Concn. of neutral salt: (*c*) 0·1000M, (*d*) 0·2000M, (*e*) 0·0500M.
Total ionic strength: (*c*) 0·14916, (*d*) 0·24916, (*e*) 0·19916.

	Salt.	KCl.	NaCl.	LiCl.	HCl.		K_2SO_4.	Na_2SO_4.
(*c*)	*k*	0·280	0·191	0·182	0·179	(*e*) *k*	0·257	0·182
	F	1·97	1·35	1·28	1·26	*F*	1·81	1·28
(*d*)	*k*	0·387	0·239	0·225	0·216			
	F	2·73	1·68	1·58	1·52			
		$K^{\cdot}$.	$Na^{\cdot}$.	$Li^{\cdot}$.	$Cd^{\cdot\cdot}$.	$Zn^{\cdot\cdot}$.	$Mg^{\cdot\cdot}$.	$Be^{\cdot\cdot}$.
$r \times 10^8$, cm.		1·33	0·95	0·70	0·99	0·83	0·75	0·30(?)

it is dependent upon the cations present in the reacting solution. Velocity constants for the reaction, at two different initial concentrations and in the presence, separately, of potassium, sodium, and hydrogen ions, were determined at four different temperatures. All glassware and thermometers were standardised, and solutions were made up at thermostat temperatures, which were constant to ±0·02°. The reaction rates in solutions containing neutral salts decreased as the reactions proceeded, the rates being relatively fast (see Part II, *loc. cit.*). The velocity constants recorded in Table III for these solutions are, therefore, extrapolated initial rates, and a detailed example is given in Table I(*b*). Those given for the other two solutions are mean values and have been re-determined; they differ only slightly from the values given in Part II.

All reaction solutions, excepting those containing hydrochloric acid, contained 0·005N-sulphuric acid. Determinations were made in slightly acid solutions because they appear to give more consistent results than neutral solutions. In order to avoid heating and contraction effects on mixing, the two reactant solutions contained equivalent chloride concentrations.

TABLE III.

Salt and concn.	28°.	25°.	20°.	15°.	*E*.	$PZ \times 10^{-7}$.
	(*a*) 0·01666N-$K_2S_2O_8$ + 0·01666N-KI + 0·005N-H_2SO_4 + RCl.					
—	0·174	0·142	0·0984	0·0683	12,500	0·361
0·3500M-KCl	0·673	0·551	0·390	0·270	12,430	1·222
0·3500M-NaCl	0·425	0·343	0·238	0·160	13,010	2·028
0·3500M-HCl	0·366	0·290	0·199	0·135	13,150	2·179
	(*b*) 0·0333N-$K_2S_2O_8$ + 0·0333N-KI + 0·005N-H_2SO_4 + RCl.					
—	0·230	0·187	0·130	0·088	12,700	0·657
0·2000M-KCl	0·528	0·430	0·298	0·205	12,680	1·453
0·2000M-NaCl	0·373	0·298	0·205	0·141	12,900	1·476
0·2000M-HCl	0·338	0·272	0·185	0·127	13,090	1·856

The velocity constants, in g.-equivs./l./min., are recorded in Table III beneath the corresponding temperatures; *PZ* values are in l./sec. The activation energies, in cals./g.-mol., were computed by plotting ln *k* against $1/T$, and straight lines were obtained in all cases. The velocity constants have the same numerical value whether expressed in terms of g.-equivs. or g.-mols. They were reduced from minute to second units, and were then used in calculating the *PZ* values from the equation $k = PZe^{-E/RT}$.

Table III shows that neutral salts, even in moderate concentrations, have a marked effect upon the velocity constant of the reaction. Since the experimental error in the estimation of *k* is approximately 1%, the variations in *E* values are too small to permit of any definite conclusions concerning the specific effects of different cations, but there is some evidence that both *E* and *PZ* increase with increasing ionic strength. This is predicted by the following considerations. One may write the Debye–Hückel equation in the form:

$$\ln k = \ln k_0 + 2\alpha_1 Z_a Z_b \sqrt{I} \times (\boldsymbol{R}DT)^{-1\cdot5},$$

where *D* is the dielectric constant, whence one obtains

$$E = E_0 - 3\alpha Z_a Z_b \sqrt{I} \times (\boldsymbol{R}DT)^{-1\cdot5} \left\{ \boldsymbol{R}T^2 \cdot \frac{\mathrm{d}}{\mathrm{d}t} \ln D + \boldsymbol{R}T \right\}$$

which, since $\alpha_1 = \alpha(\boldsymbol{R}DT)^{1\cdot5}$, is the expression given by Moelwyn-Hughes ("Kinetics of Reactions in Solution," 1933, p. 199), who points out that, for water at 25°, the two terms $\boldsymbol{R}T^2(\mathrm{d} \ln D/\mathrm{d}t)$ and $\boldsymbol{R}T$ are, approximately, −930 and 590 cals., respectively. The activation energy for the persulphate–iodide reaction should therefore increase with increase in ionic strength, since the reacting ions are of like sign.

If *E*, the activation energy, for such a reaction increases with increase in ionic strength, it follows, from the

equation $k = PZe^{-E/RT}$, that PZ, the collision factor, must do so also, since the bimolecular constant for a reaction between ions of like sign increases rapidly with increase in ionic strength. Furthermore, PZ must increase with increase in E, and this agrees with most of the examples in Table III. That there is such a functional relationship between PZ and E has been shown by Fairclough and Hinshelwood (*J.*, **1937**, 539) for a reaction in a series of solvents.

The PZ and E values for the reaction are relatively low. Since the reactants, the critical complex, and the products are polar, solvation of all three occurs, and the complex, being the most polar, is solvated to a greater degree than the reactants :

$$S_2O_8,mH_2O'' + I,nH_2O' \rightleftharpoons S_2O_8I,(m + n)H_2O'''$$

Employing the transition-state theory, Bell (*J.*, **1943**, 632) has shown that such solvation leads to low values for both PZ and E. The factor E is, evidently, the more effective in the case of the persulphate–iodide reaction and accounts for its relatively rapid rate.

PORTH, GLAM.

[*Received, December 3rd*, **1945**.]

Recent Work on Corrosion and Oxidation.

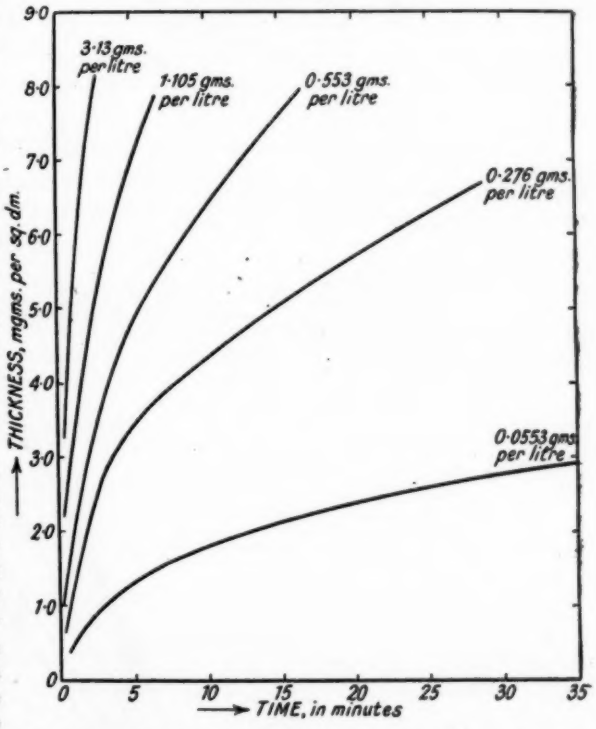
A Lecture delivered before the Chemical Society in London on October 4th, 1945.

By U. R. Evans.

Significance of the Subject to the Pure Scientist.—In view of the large amount of study devoted to combination between non-metal and non-metal, or between metal and metal, it may seem strange that so little notice is paid by pure scientists to combination between metal and non-metal. Certainly, the products of such combination, the metallic salts and compounds, receive some attention—mainly from the elementary student—but the kinetics of the combination processes are almost completely ignored both in the textbook and in the lecture room, although such processes often obey simple, well-defined laws and principles, susceptible of reasonable interpretation. The cause of this apparent unpopularity may perhaps be found in the name. Many of these reactions are, for convenience, described as " Corrosion Processes," a term which implies an unwholesome change leading to something unclean and ugly. Consequently—although the great economic and industrial importance of corrosion, which is responsible for costly damage and sometimes disastrous breakdowns, frequently forces the applied chemist and engineer to subject the phenomena to *ad hoc* research, often empirical and not always profitable—yet the pure chemist takes little or no part in this work; indeed he often remains unaware of its existence, since the results are printed in industrial journals and abstracted in the " B " series of *British Chemical Abstracts*.

Fig. 1.

Growth of iodide on silver.



Actually, the belief that products of combination of metals and non-metals are invariably ugly is hardly justified. Where the processes lead to films which display interference colours, rather beautiful effects are often met with. Oxide films on nickel show four orders of attractive interference colours (red appears four times), and when transferred from the metal to transparent plastic they still show bright tints, which are now complementary to those shown on the metal (Evans, *5th Report of Iron and Steel Institute Corrosion Committee*, 1938, p. 225). Even rust, deposited on glass or plastic, often displays bright colours by reflected light, whilst exhibiting its typical dirty yellow appearance by transmitted light.

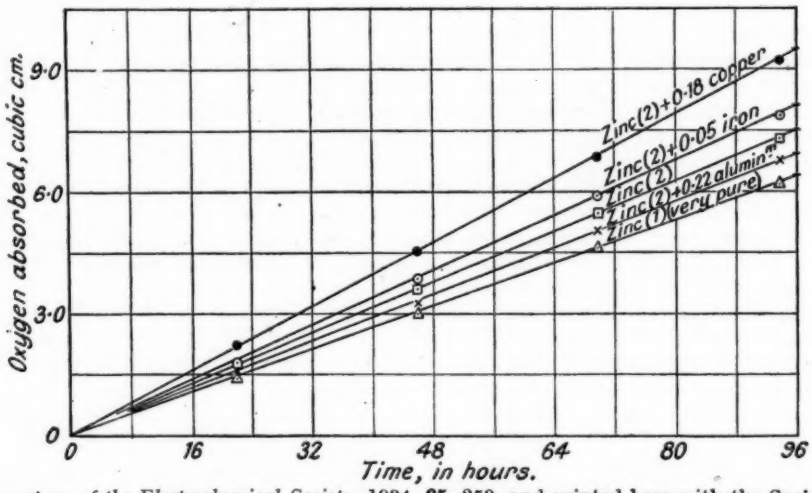
But in any case, the neglect of one of the natural divisions of Chemistry for no good scientific reason must necessarily lead to a mistaken picture of the whole, especially when the neglected reactions obey laws and principles which appear—at least at first sight—very different from those governing the familiar part of Chemistry. We cannot individually study everything, but we can at least make our collective studies a representative sample of the whole. It is hoped that, in planning instruction or research for the post-war period, chemists will bear in mind that the neglect of one division of their subject in the past affords no convincing justification for its continued neglect in the future.

Classification of Reactions.—It is not unusual to distinguish between " dry " and " wet " processes—the first being exemplified by the appearance of compact oxide scale on iron heated in air, and the second by the formation of hydrated rust on iron immersed in a salt solution containing oxygen. Such a classification is unsatisfactory; it is not logical, for instance, to separate the formation of iodide films on silver by exposure to iodine vapour (a dry process) from their formation by immersion in a solution of iodine (a wet process). Another scheme of classification distinguishes between " direct chemical combination " and " electrochemical action "; but the high-temperature oxidation of copper, formerly regarded as a typical case of direct combination, is now believed to involve migration of ions through the scale under an E.M.F.

A more satisfactory classification is a division into (*a*) film-forming reactions and (*b*) others. If a reaction converts the surface of the metal into a solid film, which isolates metal from reagent, it is likely to die away with time. If the products pass into solution, this cause of retardation is absent, although other causes (*e.g.*, exhaustion of reagent) may operate. The formation of solid silver iodide on silver immersed in a chloroform solution of iodine (Evans and Bannister, *Proc. Roy. Soc.*, 1925, *A*, **125**, 370) is a good example of a film-forming reaction; the rate of thickening dies away with time, being over the greater part of each curve (Fig. 1) inversely proportional to the thickness attained. The corrosion of zinc or its alloys partially immersed in potassium

chloride solution (Borgmann and Evans, *Trans. Electrochem. Soc.*, **1934**, **65**, 249) is an electrochemical reaction with soluble cathodic and anodic products (potassium hydroxide and zinc chloride), where there is no falling off

FIG. 2.

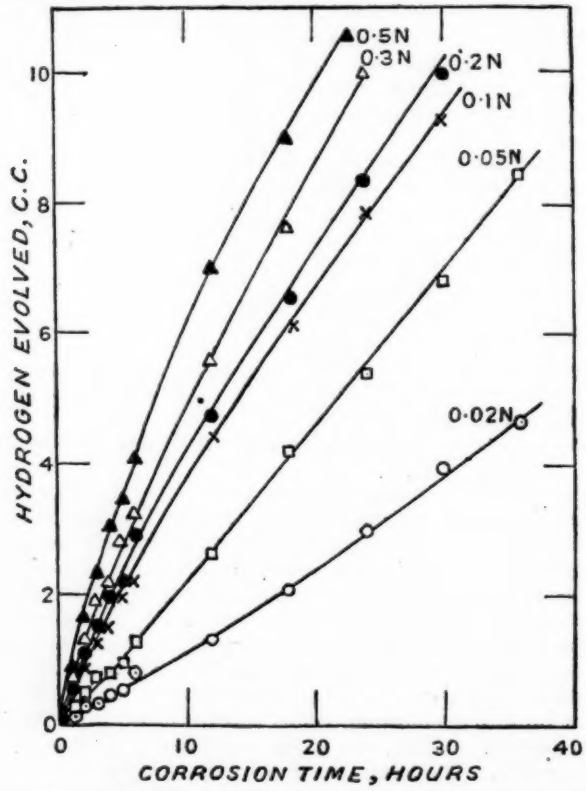


From the *Transactions of the Electrochemical Society*, 1934, **65**, 259, and printed here with the Society's permission.

of reaction with time, the curves (Fig. 2) being remarkably straight. But such processes do not invariably give straight lines; the corrosion of magnesium in sodium chloride solution (Lewis and Evans, *J. Inst. Metals*, 1935,

FIG. 3.

Effect of concentration of sodium chloride solution on corrosion.



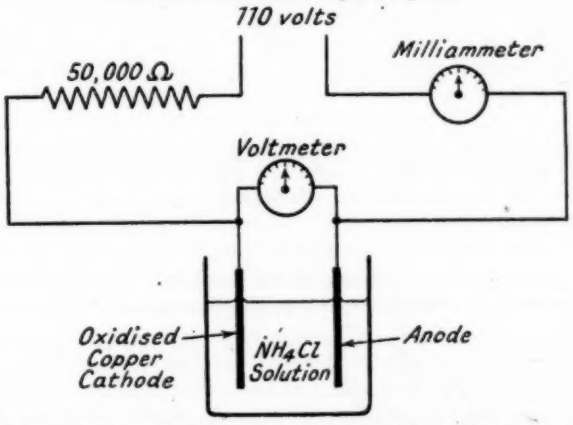
57, 231) is represented by nearly straight lines at intermediate concentrations, but not at high or low ones (Fig. 3).

Filming Reactions.

Gravimetric Study of Oxidation.—The obstructive character of oxide films is shown by the fact that most metals can be kept in fairly dry, pure air without visible change; yet change does proceed—as demonstrated gravimetrically by Vernon. The curves for the oxidation of zinc in air at ordinary temperatures (Vernon, Akeroyd, and Stroud, *J. Inst. Metals*, 1939, **65**, 301) show rather rapid change at first, falling off as the film thickens.

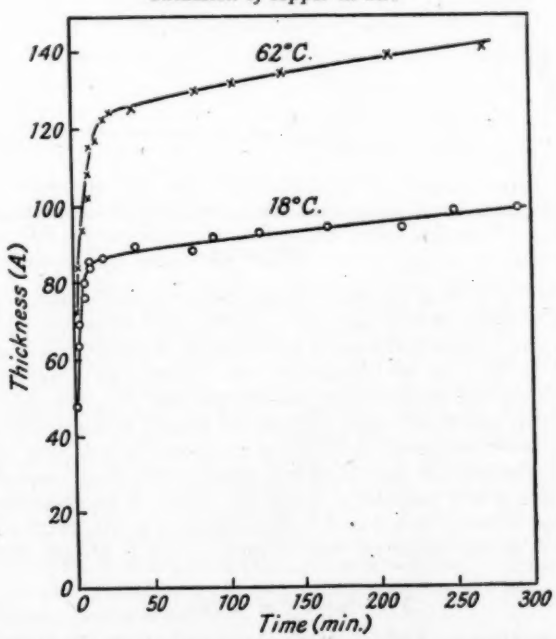
Electrometric Study of Oxidation.—For short exposures to air, it is convenient to ascertain the thickness by measuring the millicoulombs needed for the cathodic reduction of the film in ammonium chloride solution (*e.g.*, cuprous oxide to metallic copper, or ferric oxide to the ferrous condition so that it passes into solution). If the

FIG. 4.
Electrometric estimation of oxide films.



current is obtained from a high E.M.F. applied to a very high resistance (Fig. 4), its strength remains constant despite changes of resistance or back E.M.F. in the cell, and only the time need be measured to obtain the coulombage. A voltmeter or potentiometer gives the end-point, since the potential drop needed to force this constant current through the cell will increase when reduction of oxide gives place to liberation of hydrogen.

FIG. 5.
Oxidation of copper in air.



By exposure of copper or iron to oxygen for different times, and measurement of the coulombage needed for reduction, oxidation–time curves have been obtained (Evans and Miley, *Nature*, 1937, **139**, 283; *J.*, 1937, 1295). Even at ordinary temperatures, copper (Fig. 5) and iron (Fig. 6) begin to oxidise quickly, but the rate of attack

soon slows down and the metal suffers no visible change; on iron, rough surfaces develop more oxide than smooth ones. At high temperatures (Fig. 7), the oxidation is more rapid and the films soon reach thicknesses sufficient for interference colours, but there is still a marked tendency for the rate to fall off with time.

FIG. 6.

Oxidation of iron in a desiccator at 18° after different abrasions.

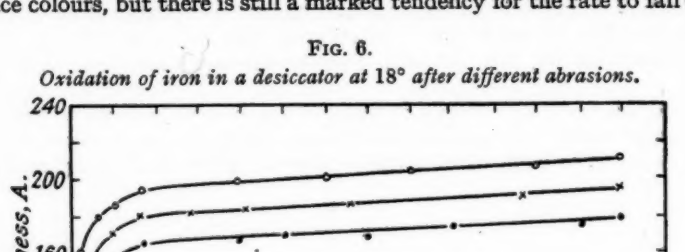
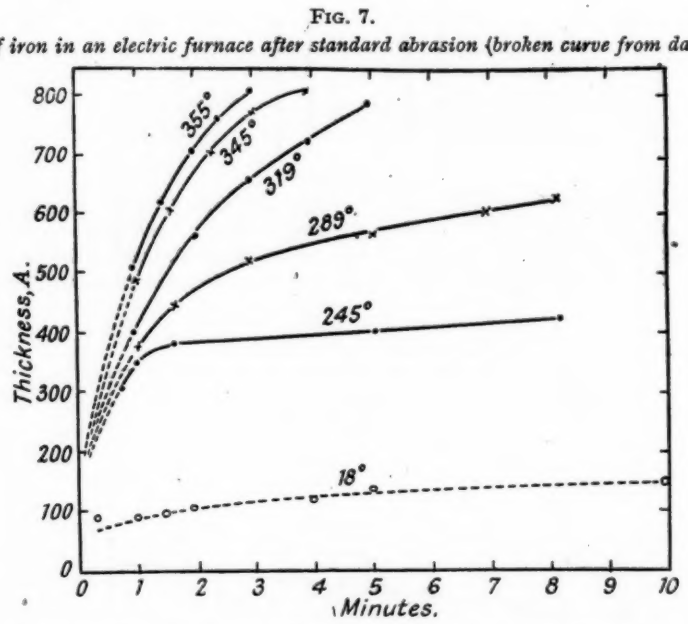


FIG. 7.

Oxidation of iron in an electric furnace after standard abrasion (broken curve from data of Fig. 6).



Oxidation of Light Metals.—This falling off with time is not invariably met with. Pilling and Bedworth (*J. Inst. Metals*, 1923, **29**, 529) calculated from specific gravities that when the ultra-light metals, potassium, sodium, calcium or magnesium, are oxidised, the oxide produced would occupy a smaller volume than the metal destroyed, and the oxide coat is likely to be porous and non-protective. Such metals burn in air, and the oxidation curve recorded by Pilling and Bedworth for calcium at 500° is a straight line. Recently Gulbransen (*Trans. Electrochem. Soc.*, 1945, **87**) has stated that magnesium gives a straight line only at high temperatures, where the metal is volatile; at lower temperatures there is an appreciable falling off of oxidation with time.

Oxidation of Heavy Metals.—The heavier metals do not readily burn in air, and yield oxidation curves which definitely fall off with time; this is not surprising, since the oxide, if unconstrained, would occupy a larger volume than the metal destroyed in producing it and is thus likely to be obstructive. Iron obeys a logarithmic equation at low temperatures (Vernon, Akeroyd, and Stroud, *J. Inst. Metals*, 1939, **65**, 321), which can be written

$$y = k_1 \log (k_2 t + k_3),$$

where y is the mean thickness at time t. At high temperatures it obeys (Portevin, Prétét, and Jollivet, *Rév. Met.*, 1934, **31**, 101, 186, 219) the well-known parabolic equation

$$y^2 = k_4 t + k_5$$

In both these equations the k's are constants independent of time but varying with temperature. Zinc, which has a low melting point, was found by Vernon and his colleagues to conform to the logarithmic law throughout the solid range.

The lecturer believes that the logarithmic equation is due to discrete mechanical breakdowns of the film due to the compressional stresses arising from the volume relation mentioned above. The wrinkling of the film observed when it is freed from constraint by the anodic undermining of the metal to which it is attached (Evans and Stockdale, J., 1929, 2651) testifies to the real existence of these compressional stresses, and it has been shown that such discrete breakdowns can lead to the logarithmic relationship (Evans, *Trans. Electrochem. Soc.*, 1943, **83**, 335).

The parabolic law is generally regarded as due to lattice imperfections in the oxide films, which at high temperatures become semi-conductors; the existence of these defects provides a means for the passage of metal cations outwards, accompanied by electrons, to meet the oxygen. Experimental evidence of the passage of metal outwards through the film in such cases has been furnished by Pfeil (*J. Iron Steel Inst.*, 1929, **119**, 520) and by Wagner (*Z. physikal. Chem.*, 1933, *B*, **21**, 37). Sulphide films, where the defects are more numerous, allow appreciable transport to take place at lower temperatures than oxide films; copper exposed to air containing hydrogen sulphide develops the same sequence of colours at ordinary temperatures as is developed at high temperatures in pure air. The presence of imperfections is shown by the fact that cuprous sulphide and ferrous sulphide contain less metal than the formulæ Cu_2S and FeS would indicate; the mineral, pyrrhotite, has been assigned the formula $Fe_{11}S_{12}$ in some mineralogical textbooks, but is best regarded as FeS with about 1/12 of the cation sites vacant, and with about $\frac{1}{6}$ of the cations in the ferric state, so as to maintain electrical neutrality.

The Electrical Basis of the Oxidation Constant.—The constant of the parabolic equation should, according to the conception of transport by lattice defects, be represented by Wagner's expressions, of which the simplest form (which neglects variation of conductivity with pressure) is

$$k_4 = [2Jn_e(n_c + n_a)\kappa E]/DF$$

where κ is the specific conductivity, n_e, n_c and n_a the three transport numbers representing the share taken by electrons, cations and anions in transporting electricity, F Faraday's number, J the equivalent weight of the film substance (whether oxide, sulphide, iodide or other compound), D its density, and E the E.M.F. of the cell metal/non-metal. An instructive derivation of these expressions has been provided by Hoar and Price (*Trans. Faraday Soc.*, 1938, **34**, 876), and a simple exposition of the mechanism of film growth by Price (*Chem. and Ind.*, 1937, 769).

Only in three cases of film growth are the transport numbers known. Here, the observed and calculated values of the velocity constant show good agreement (see table), although the values of k in different cases are of different orders of magnitude. The velocity constant k used in the table is equal to $k_4D/2J$.

Calculated and experimental values of the constant k, as defined by the equation $d\eta/dt = k/y$, *where* η *is the amount of oxide, sulphide or iodide in g.-equivs. per sq. cm.*

(Tabulated by L. E. Price from papers by C. Wagner.)

Reaction.	Temp.	Calc.	Exptl.
$2Cu + I_2 = 2CuI$	195°	$3{\cdot}8 \times 10^{-10}$	$3{\cdot}4 \times 10^{-10}$
$4Cu + O_2 = 2Cu_2O$	1000	6×10^{-9}	7×10^{-9}
$2Ag + S = \alpha Ag_2S$	220	$2\text{–}4 \times 10^{-6}$	$1{\cdot}6 \times 10^{-6}$

Improvement of Oxidation Resistance by Selective Oxidation Treatment.—Price and Thomas (*J. Inst. Metals*, 1938, **63**, 21), studying the numbers for the oxidation resistance of copper alloys obtained by Fröhlich (*Z. Metallk.*, 1936, **28**, 368), noted that qualitatively the results fitted the electrical theory of oxidation, since the addition of metals like aluminium and beryllium, whose oxides had high electrical resistance, enhanced the oxidation resistance of copper, whereas metals with oxides of low resistance conferred little benefit. Quantitatively, however, theory and observation seemed to clash. If the protective film on copper–aluminium alloys were pure alumina, the improvement should be at least 80,000 times (transport numbers being in doubt, an exact prediction was impossible); Fröhlich's measurements, however, showed an improvement of only 36.

Price and Thomas attributed this discrepancy to the presence of copper oxide in solid solution, which would diminish the resistance of the alumina, and expressed the view that pure alumina films—if obtained—would afford the theoretical improvement. They heated a copper alloy containing 5% of aluminium in hydrogen containing a trace of water vapour (corresponding to 0·1 mm. mercury pressure)—a treatment designed to oxidise aluminium, a metal with extremely high affinity for oxygen, but not copper. This treatment left the alloy unchanged in appearance, but evidently a protective film had been produced, since on being heated for 4 hours at 800° in oxygen, the specimen still remained unchanged in appearance, although an untreated specimen of alloy, heated in oxygen (for the same time and at the same temperature) became greatly blackened. Quantitative experiments showed that the treatment gave an improvement of 200,000 times, which compares reasonably with the prediction of theory (at least 80,000).

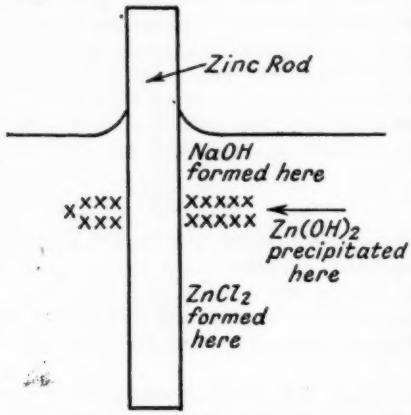
This process, known as " selective oxidation," not only provides a means of greatly improving the resistance of copper alloys to high-temperature oxidation in unpolluted air, but also the resistance of silver towards tarnishing in air containing sulphur compounds—a change which, for reasons given above, occurs at ordinary temperatures.

Non-Filming Reactions.

Action of Salt Solutions on Heavy Metals in Presence of Oxygen.—A solution of oxygen in pure water is likely to produce a layer of sparingly soluble oxide or hydroxide on the metal, and the attack will usually be unimportant—although exceptions could be cited. If, however, a salt is present in the water, electrochemical changes—often leading to freely soluble anodic and cathodic products—become possible, provided that the surface is not equipotential. In practice, some factor is usually present to produce a flow of currents between different parts of the metal. Clearly, if the specimen consists of two metals in contact, relatively strong currents may be expected. However, a single metal, if locally deformed, may generate currents, the deformed portion being usually anodic to the rest. Alternatively, if the oxide film or scale covering the surface is locally discontinuous, the bare metal will be anodic. Even an ideally uniform metallic specimen partly immersed in solution with air above will generate a current, the part near the water-line being usually the cathode, since oxygen, a cathodic stimulator, can here be replenished most readily. A few typical cases of electrochemical corrosion are discussed below.

FIG. 8.

Effect of vertical zinc plate or rod partially immersed vertically in sodium chloride solution.

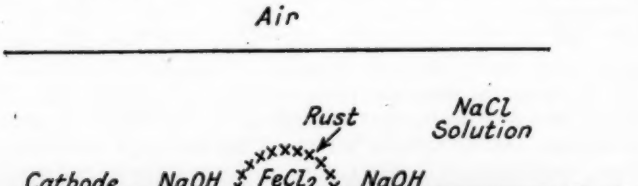


Zinc Rod Partially Immersed in a Salt Solution (Fig. 8).—If zinc is partially immersed in a solution of sodium chloride, oxygen at the water-line zone will be converted by the cathodic reaction into OH' ions, whilst, a little lower down, zinc will suffer anodic attack providing $Zn^{\cdot\cdot}$ ions. The cathodic and anodic products can be regarded as sodium hydroxide and zinc chloride respectively, and will give zinc hydroxide, often in a membranous form, at the level where they meet. The reaction is thus the combination of zinc, oxygen and water to form zinc hydroxide, but it will be noticed that zinc is destroyed at *one* point, oxygen taken up at a *second*, and zinc hydroxide precipitated at a *third*. Clearly, although the zinc hydroxide is sparingly soluble, it will not, for geometrical reasons, give protection to the metal, and attack will continue without stifling itself (cf. Fig. 8). This is the main danger of electrochemical attack; it often leads to freely soluble substances as the primary products, and the secondary product, although sparingly soluble, appears out of physical contact with the seat of attack. Where one of the primary products is sparingly soluble, even electrochemical action is retarded or prevented, as shown later.

Iron Covered with Discontinuous Mill-scale in Salt Solution below Air (Fig. 9).—Steel leaves the rolling mill covered with a thick oxide scale, usually discontinuous. If placed in sodium chloride solution, the metal exposed at a hole in the scale will be anodic to the scale, the current being usually controlled by the rate of supply of oxygen to the mill-scale around the hole, which forms the cathode. Since the cathode is relatively

FIG. 9.

Corrosion at breaks in oxide scale on iron immersed in sodium chloride solution.



large, the rate of arrival of oxygen and consequently the current strength will be considerable, but its whole effect will be concentrated on the small anode (the iron exposed), so that the intensity of attack (the corrosion per unit area of the part affected) will be serious, and " pits " may be quickly produced at holes in the scale. A membrane of rust (Fe_2O_3, H_2O) is usually formed over each pit, where anodic and cathodic products meet. The removal of mill-scale usually diminishes the rate of penetration into a steel plate or pipe and consequently the risk of perforation, although the total attack may sometimes be increased.

Iron Covered with a Discontinuous Coating of Copper.—A continuous coating of copper will largely protect steel against attack, but if the copper is scraped away locally, exposing the steel, the dangerous combination of large cathode (the copper) and small anode (the exposed steel) arises, and intense local attack develops; electrochemical considerations indicate that under some, but not all, conditions, the attack will be more intense than if no copper were present; this intensification has been realized in the laboratory (for instance, Evans, *J. Inst. Metals*, 1928, **40**, 99).

Iron Covered with a Discontinuous Coating of Zinc.—If the coating is of zinc, a metal anodic to iron, the iron

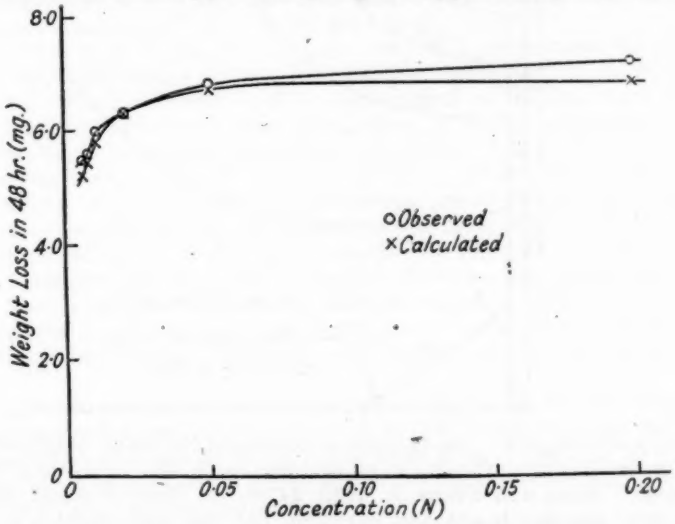
exposed at a gap may receive cathodic protection, provided that the gap is not too wide. The protection of iron is achieved at the expense of the zinc, but it is better for the attack to proceed sideways instead of downwards, especially as this will reduce the chance of a fatigue crack developing. Zinc is often applied by dipping steel into the molten metal, or by electro-plating, or again by spraying (" metallization "). Lately it has become a practical proposition to apply it as paint, and experiments at Cambridge show that paint coats containing 95% of metallic zinc held together with polystyrene can be obtained, and give good protection against sea-water, even when applied to a rusty surface, since the zinc reduces the rust, and builds a conducting bridge to the iron below it. Rusty iron, coated with zinc-rich paint, and pierced with a scratch-line exposing the bright metal, has been kept in sea-water for two years without the development of fresh rust (Mayne and Evans, *Chem. and Ind.*, **1944**, 109; Evans, *Met. Ind., London*, **1945**, **67**, 114).

Quantitative Demonstration of the Electrochemical Character of Corrosion.—The currents flowing between anodic and cathodic areas on naturally corroding specimens have a real existence. They have been detected and measured by four independent methods, and were found strong enough to account for the amount of corrosion actually observed. The four methods are severally described in the following papers: Evans and Hoar, *Proc. Roy. Soc.*, **1932**, *A*, **137**, **343**; Thornhill and Evans, J., **1938**, 614; Brown and Mears, *Trans. Electrochem. Soc.*, **1938**, **74**, **495**; **1942**, **81**, 455; Agar, reported by Evans, *J. Iron Steel Inst.*, **1940**, **141**, 221P.

Only the first and last of these will be considered. The method developed by Hoar depended on the availability, through the kindness of the late Dr. W. H. Hatfield, of a steel so uniform as to give reproducible distribution of anodic and cathodic areas on partial immersion in salt solutions. Specimens were cut along the

FIG. 10.

Corrosion of iron in potassium chloride solution (a) *observed by weight loss,* (b) *calculated from purely electrical data* (T. P. Hoar).



dividing line, and the two halves mounted in their correct position partially immersed in salt solution and joined to an external source of current. The cathode potential drop was measured and plotted against the current passing. Having obtained this relation, Hoar took uncut specimens, and, by measuring the cathode potential drop, was able to ascertain the current flowing and thus, on division by Faraday's number, to calculate the corrosion; this was found to agree well with the corrosion experimentally determined by loss of weight (Fig. 10).

The most recent method, used by Agar just before the war in his study of zinc partially immersed in salt solution, depends on the plotting of equipotential lines (Fig. 11); if the specific conductivity of the liquid is known, the distance between the equipotentials provides, on application of Ohm's law, a means of estimating the current. Calculation from the electrochemical data accounted for the whole of the corrosion below the water-line; a small amount of corrosion on the zone wetted by creepage above the water-line may have had a different origin, but the outbreak of hostilities interrupted the research before this matter had been fully investigated.

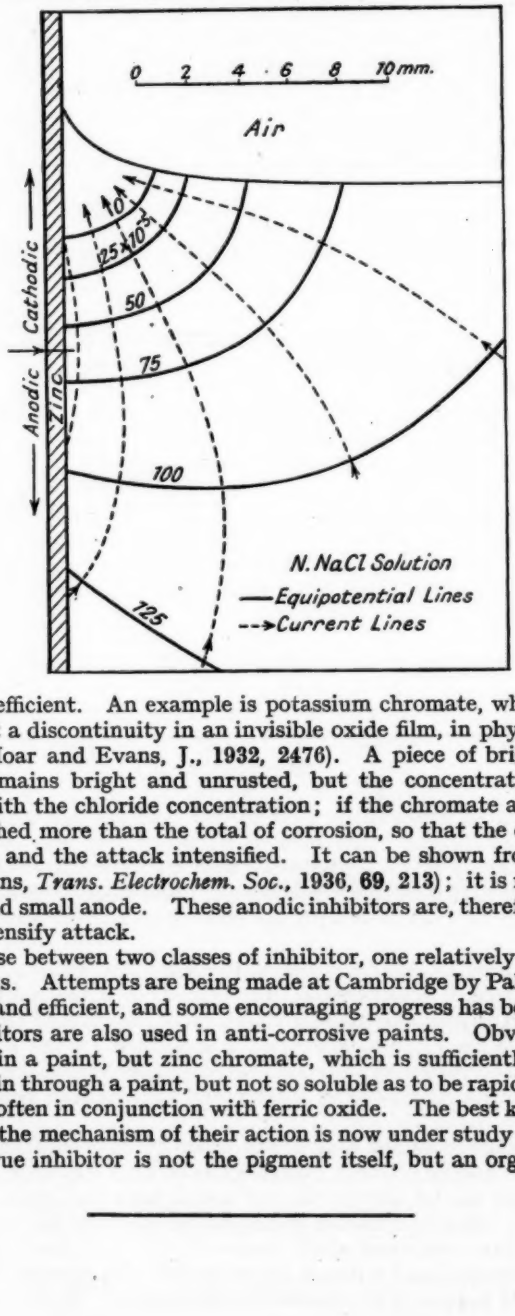
Soluble Inhibitors.—If a water contains a sufficient quantity of a substance yielding a sparingly soluble substance either as cathodic or anodic product, even electrochemical corrosion will stifle itself. Thus we have two classes of soluble inhibitors, known as cathodic and anodic inhibitors respectively.

An important example of a cathodic inhibitor is calcium bicarbonate, which is present in most hard natural waters. It is the presence of this compound which makes it possible to carry these waters through steel pipes without their emerging red with rust, and without the objectionable property of producing red stains on white articles washed in it—as would happen if ferrous salts were present. As soon as these waters begin to act on

iron, the rise of pH value at the cathodic surface causes the precipitation of calcium carbonate, which coats the cathodic areas and smothers the cathodic reaction. Although subsequently the calcium carbonate interacts with iron salts formed in the incipient anodic reaction to give a clinging form of rust, this rust has considerable protective action, and keeps the rate of corrosion far below that produced by soft waters. A water containing carbonic acid in excess of the amount needed to hold the calcium carbonate in solution will not at once throw down a film, and will therefore produce serious attack on steel pipes, emerging either rusty or (worse still) containing ferrous salts. If passed through a bed of limestone or calcined dolomite—to convert the excess carbonic acid into calcium bicarbonate—such waters often become suitable for pumping through steel pipes. Nevertheless, these inhibitors are not entirely efficacious, and will produce rust on bright, freshly abraded steel.

FIG. 11.

Potential distribution and current flow around zinc with sodium chloride (J. N. Agar).



Anodic inhibitors are more efficient. An example is potassium chromate, which serves to precipitate any trace of ferrous salts, formed at a discontinuity in an invisible oxide film, in physical contact with the metal, thus healing the " leakage " (Hoar and Evans, J., 1932, 2476). A piece of bright, abraded steel, placed in water containing chromate, remains bright and unrusted, but the concentration of chromates needed for complete inhibition increases with the chloride concentration; if the chromate added be insufficient, the area suffering attack will be diminished more than the total of corrosion, so that the corrosion per unit area of the part affected will be increased, and the attack intensified. It can be shown from electrochemical principles that this is to be expected (Evans, *Trans. Electrochem. Soc.*, 1936, **69**, 213); it is really another example of the combination of large cathode and small anode. These anodic inhibitors are, therefore, dangerous, since if added in insufficient amount, they intensify attack.

We have, therefore, to choose between two classes of inhibitor, one relatively safe but inefficient, the other relatively efficient but dangerous. Attempts are being made at Cambridge by Palmer to work out an inhibitive system which will be both safe and efficient, and some encouraging progress has been made.

Inhibitive Pigments.—Inhibitors are also used in anti-corrosive paints. Obviously potassium chromate is too soluble to be incorporated in a paint, but zinc chromate, which is sufficiently soluble to confer inhibitive properties on moisture soaking in through a paint, but not so soluble as to be rapidly washed away, is a common component of priming paints—often in conjunction with ferric oxide. The best known inhibitive pigments are, however, lead compounds, and the mechanism of their action is now under study at Cambridge by Mayne, who has found that generally the true inhibitor is not the pigment itself, but an organic compound, such as lead linoleate.

OBITUARY NOTICES.

THOMAS J. NOLAN.

1888—1945.

THOMAS JOSEPH NOLAN was born on November 9th, 1888, and received his early education at the Christian Brothers' Schools in Dublin. After making marked progress in science he gained the Archbishop Walsh University Scholarship, and entered University College, Dublin, in 1906. Three years later he obtained the B.A. degree with first class honours in chemistry and experimental physics and was awarded an Exhibition. Nolan commenced research work in University College, Dublin, under the late Professor Hugh Ryan, and, during the two years following graduation, he was senior demonstrator in chemistry and a teacher of chemistry in the City of Dublin Technical Schools. He was then awarded the travelling studentship in chemistry of the National University of Ireland for work on the higher ketones and secondary alcohols derived from the amides of palmitic and stearic acids, subsequently published in the *Proceedings* of the Royal Irish Academy. In 1912, he obtained the M.Sc. degree of the National University with first class honours in chemistry.

In the autumn of 1911, Nolan commenced research work in Geneva under Amé Pictet on the constitution of *iso*strychnine, and the use of methylal in ring syntheses. Owing to the illness of Pictet this work was not completed, and Nolan went to London, where his work under Samuel Smiles on the isomerism of the sulphides of β-naphthol was embodied in a series of five papers in the *Proceedings* and *Transactions* for 1912 and 1913.

Nolan worked under Zincke in Marburg in 1913, and published in the *Annalen* a paper on the action of nitric acid on 3 : 5 : 6-trichloro-*o*-cresol. Later in the same year, he went to the Kaiser Wilhelm Institüt in Berlin where, working under Willstätter, who held him in high esteem, he isolated and established the constitutions of the colouring matters of the rose and the peony.

With the outbreak of the First World War, Nolan broke off his investigations and returned to Dublin, where he was awarded the D.Sc. degree of the National University. In the following year he joined the Research Staff of Messrs Nobel's Explosives Co., Ltd., and carried out research work on the manufacture and utilisation of nitro compounds and their by-products, and, later, on the manufacture of fine chemicals, including acriflavine, phthalic anhydride, and dimethylaminobenzaldehyde. In 1917, he was placed in charge of confidential research on the manufacture of propellant powders; this work led to the manufacture of a new stabilised propellant powder (" Ardeer Cordite ") made without the aid of a volatile solvent.

On the amalgamation of the various explosives companies in 1919, Nolan was appointed chemist in charge of development work in propellants. He developed several new types of sporting powders (including " Improved Ballistite " and " Semi-Smokeless Powder "), and a series of powders of the nitro-cellulose type (" Nobel Neonites "). In 1924, he directed for Imperial Chemical Industries a detailed research into the production of " tetryl," and several novel features suggested by him were incorporated in the manufacturing plant. In 1925, he was sent by Imperial Chemical Industries to Czechoslovakia to report and advise on the manufacture of explosives.

While working on industrial and military explosives, Nolan kept in touch with general organic chemistry, and, when a biochemical research department was opened in 1922, studied the possible uses of kojic acid as a raw material for the production of synthetic drugs. Four years later, in conjunction with Professor (later, Sir) Robert Robinson, he published in the *Journal* a synthesis of peonidin chloride, the anthocyanidin of the peony, which confirmed the constitution which he had suggested in 1915.

In 1925, Nolan succeeded Dr. J. Reilly as assistant State Chemist in Dublin. Six years later he became State Chemist. While in the State Laboratory he published two papers in the *Proceedings* of the Royal Irish Academy on the pigments of the elderberry.

In 1932, Nolan was appointed Professor of Chemistry in University College, Dublin, in succession to the late Professor Hugh Ryan. During his thirteen years as professor, he carried out and directed extensive researches, published in a long series of papers in the *Scientific Proceedings* of the Royal Dublin Society, on the chemical constitution of products isolated from Irish lichens. In this field, he was the first to isolate a chlorinated depsidone, gangaleoidin, and in the last few years he succeeded in isolating two nitrogenous substances from the lichen *Lecanora epanora*.

Nolan was elected a Fellow of the Chemical Society in 1913, and served on the Council from 1926 to 1929; from 1939 until his death, he was the Local Representative of the Society in Eire. He became a Fellow of the Institute of Chemistry in 1918 and, in the same year, was admitted a member of the Royal Irish Academy, serving on its Council from 1927. He joined the Royal Dublin Society in 1925, served on the Science Committee from 1926 to 1931 and, from June 1931 to the time of his death, he was on the Science Section of the Council. While holding the chair of chemistry in University College, Dublin, he was a member of the Governing Body of the College and, later, of the Senate of the National University of Ireland. He represented the Irish Government at the World Power Congress in 1936 and University College, Dublin, at the London University Centenary Celebrations in the same year. As chairman of the Board of the Industrial Alcohol Factories, set up by the Irish Government, and as a member of the Irish Industrial Research Council and of the Irish Medical Research Council, he was frequently consulted by manufacturers and others on chemical matters arising out of the shortages of imported raw materials and finished goods during the last six years.

Nolan's death on March 12th, 1945, at the early age of fifty-seven, came as a great shock to his colleagues, research workers, and students. He had a high reputation, both as a chemist and as a professor. He ably encouraged and directed his younger research workers, and was noted for the excellence and clarity of his lectures. Despite the very large increase in the number of students taking chemistry in University College, Dublin, during his term of office, he maintained a personal contact with all of them after they had left the University. He leaves a wife and five children.

D. Reilly.

PRAFULLA CHANDRA RAY.

1861—1944.

The death of Sir Prafulla Chandra Ray at the University College of Science, Calcutta, India, on June 16th, 1944, at the age of 83 deprived the Society of a very distinguished Fellow and India of one of her foremost scientific pioneers and leaders, who was held in high esteem and sincere affection.

Prafulla Chandra Ray was born on August 2nd, 1861, in a village in the district of Khulna, Bengal. His father, Haris Chandra Ray, was a landed proprietor. Till the age of nine, Prafulla Chandra was educated in the village school founded by his father. He then entered the Hare School and, later, the Albert School at Calcutta whither the family had migrated. While at Hare School he had a severe attack of dysentery. He recovered, but was a chronic sufferer from this malady, his constitution remaining always very delicate. In 1879 he passed the Entrance Examination of the Calcutta University and entered the Metropolitan Institution founded by the late Pundit Iswar Chandra Vidyasagar, a great philanthropist, social reformer, and pioneer of advanced English education in Bengal. At that time the Metropolitan Institution had no science classes or laboratories and Prafulla Chandra, desiring a scientific career, had to attend lectures in physics and chemistry at the Presidency College, Calcutta. Here he was specially attracted by the chemistry courses of Professor (later Sir) Alexander Pedler. It was Pedler who first awakened his interest in natural science. While taking the science course for the B.A. Degree, he was awarded in 1882 one of the two Gilchrist Scholarships after an all-India competitive examination. Without completing the course for his degree, Prafulla Chandra Ray proceeded to the United Kingdom for further study and entered the University of Edinburgh. In Chemistry, he was a pupil of Professor Alexander Crum Brown, F.R.S., noted for his philosophical outlook and engaging personality. Alexander Smith and James Walker were his fellow students. He obtained the B.Sc. degree in 1886, and the Doctorate in Science in 1887. In the latter year, he was awarded the Hope Prize and served as Vice-President of the Edinburgh University Chemical Society.

On his return to India in 1889, he was appointed Assistant Professor of Chemistry at the Presidency College, Calcutta. He held this position till 1911, becoming Senior Professor for the remainder of his service under the Government. Within a short time, his reputation as a successful and inspiring teacher became widely known, and his lecture theatre was always crowded with enthusiastic chemistry students and others, attracted by the personality of the lecturer. His lectures had a great influence upon his pupils and inspired students with a spirit of enquiry and love of truth. The Professor took special delight in narrating the life and work of the great leaders in chemistry. We, his pupils, still remember his animated account of the pilgrimage of Wöhler from Germany to the great Swedish savant, Berzelius, and the vivid description of the latter's "kitchen-laboratory." At the same time, a band of devoted workers gradually gathered round him, and the chemical laboratory of the Presidency College, though rather ill-equipped judged by standards in Europe, became an important centre of original chemical investigations.

In 1896, he published his first important paper concerning the preparation of mercurous nitrite, a fairly stable compound, which, it was previously believed, could not exist. This was soon followed by a large number of papers on nitrites and hyponitrites of various metals and their decomposition by heat, as well as on nitrites of ammonia and organic amines, which represented the results of long, painstaking, and thorough work. The late Professor H. E. Armstrong, once writing about him, described him as "Master of the Nitrites." Thus, an Indian School of Chemistry was created with Prafulla Chandra Ray as its leader.

After a service of about thirty years Sir Prafulla retired from the Presidency College in 1916, and joined the University College of Science, established out of a great benefaction from the late Sir Tarak Nath Palit, as its first Palit Professor of Chemistry. Here, in a more congenial atmosphere, assisted by a continuous stream of devoted workers, he turned his attention to new investigations, notably, the co-ordination compounds of gold, platinum, iridium, and other metals with mercaptyl radicals and organic sulphides, and a number of papers were published on the subject, most of which appeared in the Journal of the Indian Chemical Society.

In 1902, he published the first volume of the *History of Hindu Chemistry*, followed by a second volume in 1908. This is the only authoritative work on the subject, and is a valuable contribution to the history of science. The work was inspired by the great French chemist Berthelot, and represents nearly ten years' painstaking search through obscure and ancient Sanskrit manuscripts and through papers on Indian history by orientalists. It is a monument of scholarship and of sound judgment on problems of Indian history, but its contents remain practically unknown even to Indian scholars on account of the highly technical nature of its presentation. Professor Prafulla Chandra Ray long cherished hopes of writing a popular edition but

could never take it up seriously owing to his other preoccupations; perhaps some of his pupils will undertake this work.

In 1936, at the age of 75, he retired from active service and became Professor Emeritus. Long before that, on the completion of his 60th year in 1921, he made a free gift of his entire salary to the Calcutta University from that date onward, to be spent for the furtherance of chemical research, and the development of the Department of Chemistry in the University College of Science.

Outweighing his achievements as a scientific worker, the creation and fostering of an Indian School of Chemistry will ever remain his conspicuous contribution towards the national progress of Indians. The Indian Chemical Society which came into being in 1924, mainly through his inspiration and the help and service of his former pupils, and of which he was the Founder President for the first two terms, constitutes another very important contribution of Prafulla Chandra Ray to the advancement of science in India.

Realising that the appalling poverty of Indian masses can only be ameliorated through the economic advancement of the country by the development of industries on scientific lines, he risked his own small income to start, in 1893, a private firm under the name of the Bengal Chemical and Pharmaceutical Works which formed the nucleus of a chemical industry in India. Subsequently, in 1902, it was made into a limited company, which, under his able guidance and advice, has rapidly grown to its present prosperous condition. It rendered very good services to the Government during the two great wars, especially during the first. He also associated himself either as promoter, patron, director, or adviser with many other industrial concerns of the country.

He received the honorary degree of D.Sc. from the University of Durham in 1912, from Dacca in 1936, and that of Ph.D. from Calcutta in 1908. The University of Benares also conferred on him a similar honorary degree. He was made a Companion of the Order of the Indian Empire in 1911 and received the Order of Knighthood in 1917. He was Honorary Fellow of the Chemical Society and of the Deutsche Akademie, München. He was President of the Indian Science Congress in 1920.

Besides being a chemist by choice and profession, Prafulla Chandra Ray had a profound interest in literature, history, and philosophy. Shakespeare, Tagore, and Madhusudan Dutt (a Bengali poet of the nineteenth century) were his favourite poets, from whose works he could quote extensively. He was also very fond of the writings of Emerson and Carlyle; a copy of Emerson's Works was a constant companion. He contributed articles in Bengali to many monthly magazines, particularly on scientific topics, and his writings were eagerly read. He published the first volume of his autobiography *Life and Experience of a Bengali Chemist* in 1932, and dedicated it to the youth of India, with the hope of stimulating their activities. The second volume of this work was issued in 1935. In reviewing this book in *Nature*, Professor H. E. Armstrong wrote: "From beginning to end the message of the book is one of the highest endeavour—pulsating with vitality and intellectual force."

Possessed of a highly sensitive and sympathetic disposition, and born in a land whose people were struggling against enormous odds for existence, Prafulla Chandra Ray could not have lived the cloistered life so congenial to his temperament. We, therefore, find him an earnest social reformer and social worker, always ready to come to the relief of his suffering countrymen liable to be stricken by such natural visitations as flood, famine, fire, etc. In 1923, Northern Bengal was overwhelmed by a flood of unusual dimensions rendering millions homeless and starving. With remarkable promptitude, Prafulla Chandra Ray organised the Bengal Relief Committee, which collected nearly 2·5 million rupees in cash and kind which was distributed in the affected area through a network of properly manned and organised relief centres. His charity was not bounded by any consideration of personal comfort or well-being. He gave away freely for the poor and, particularly, for the benefit of poor students of whom he was a great friend. He loved his pupils and took a great pride in their success.

In spite of his small income, his large and unostentatious charity was made possible by the voluntary poverty he imposed on himself. Prafulla Chandra Ray was a bachelor and made a corner room in the University College of Science his home. His mode of life was characterised by spartan simplicity and he had complete indifference to dress and conventionalities. He mixed freely with all—young and old, learned and illiterate—and was loved by all. He was always at home with people in humbler walks of life and felt somewhat ill at ease in society. He was methodical in his work and could not tolerate the least waste of any material whether in the home or in the laboratory. A gas burner left burning, a water tap left running, a filter paper soiled or a lamp burning unnecessarily in a room would make him indignant enough to shower a volley of reproaches on the offender. His punctuality was almost proverbial and his daily programme was rigidly controlled. He implanted, so to say, modern rationalistic western methods in a framework of oriental culture and habits. He never enjoyed good health, but a strong will power made possible a "life overfull of action."

On the occasion of his seventieth Birthday Celebration the Indian Chemical Society presented to him a Commemoration Volume of its Journal containing contributions from many distinguished European and Indian scientists. A similar volume together with an Address on behalf of the people of Bengal was also presented to him at the time. His eightieth birthday was celebrated by the University of Calcutta when he received a large number of addresses from educational, scientific, and industrial organisations of the country.

No truer words about the life and character of Prafulla Chandra Ray and their influence upon his country-

men can be said than those so beautifully spoken by the late poet, Tagore, when presiding over his Seventieth Birthday Celebration : " It is stated in the *Upanishads* that The One said, ' I shall be Many.' The beginning of Creation is a move towards self-immolation. Prafulla Chandra has become many in his pupils and made his heart alive in the hearts of many. And that would not have been at all possible had he not unreservedly made a gift of himself. The power of creation having its inception in self-sacrifice, is a divine power. The glory of this power in Prafulla Chandra as teacher will never be worn out by decrepitude. It will extend further in time through the ever-growing intelligence of youthful hearts; by steady perseverance they will win new treasures of knowledge."

This notice may be concluded by the words of the late Sir T. E. Thorpe when he wrote about Prafulla Chandra nearly a quarter of a century ago : " India's elevation will not come in Sir Prafulla Chandra Ray's time. A small, spare man in feeble health and a confirmed dyspeptic, he will be spent in her service. But the memory of these services will survive."

J. N. MUKHERJEE.

The General Physical Constants.

(Reprinted by permission from the paper by R. T. Birge in *Reports on Progress in Physics*, 1941, **8**, 90.)

TABLE *a*.

*Principal Constants and Ratios.**

Velocity of light	$c = (2{\cdot}99776 \pm 0{\cdot}00004) \times 10^{10}$ cm. sec.$^{-1}$.
Gravitation constant	$G = (6{\cdot}670 \pm 0{\cdot}005) \times 10^{-8}$ dyne cm.^{2} g.$^{-2}$.
Litre (= 1000 ml.)	$l = 1000{\cdot}028 \pm 0{\cdot}002$ cm.^{3}.
Volume of ideal gas (0° C., A_0)	$V_0 = (22{\cdot}4146 \pm 0{\cdot}0006) \times 10^3$ cm.^{3} atmos. mol.$^{-1}$.
	$V_0' = 22{\cdot}4140 \pm 0{\cdot}0006$ litre atmos. mol.$^{-1}$.
Volume of ideal gas (0° C., A_{45})	$V_{45} = (22{\cdot}4157 \pm 0{\cdot}0006) \times 10^3$ cm.^{3} atmos. mol.$^{-1}$.
	$V_{45}' = 22{\cdot}4151 \pm 0{\cdot}0006$ litre atmos. mol.$^{-1}$.
International ohm (= p abs. ohm)	$p = 1{\cdot}00048 \pm 0{\cdot}00002$.
International ampere (= q abs. amp.)	$q = 0{\cdot}99986 \pm 0{\cdot}00002$
Atomic weights (see table *a'*)	
Standard atmosphere	$A_0 = (1{\cdot}013246 \pm 0{\cdot}000004) \times 10^6$ dyne cm.$^{-2}$ atmos.$^{-1}$.
45° atmosphere	$A_{45} = (1{\cdot}013195 \pm 0{\cdot}000004) \times 10^6$ dyne cm.$^{-2}$ atmos.$^{-1}$.
Ice-point (absolute scale)	$T_0 = 273{\cdot}16 \pm 0{\cdot}01°$ K.
Joule equivalent	$J_{15} = 4{\cdot}1855 \pm 0{\cdot}0004$ abs.-joule cal.$_{15}^{-1}$.
Joule equivalent (electrical)	$J'_{15} = 4{\cdot}1847 \pm 0{\cdot}0003$ int.-joule cal.$_{15}^{-1}$.
Faraday constant	
(1) Chemical scale:	
	$F = 96501{\cdot}_2 \pm 10$ int.-coul. g.-equiv.$^{-1}$.
	$= 96487{\cdot}_7 \pm 10$ abs.-coul. g.-equiv.$^{-1}$.
	$= 9648{\cdot}7_7 \pm 1{\cdot}0$ abs.-e.m.u. g.-equiv.$^{-1}$.
	$F' = Fc = (2{\cdot}89247 \pm 0{\cdot}00030) \times 10^{14}$ abs.-e.s.u. g.-equiv.$^{-1}$.
(2) Physical scale:	
	$F = 96514{\cdot}_0 \pm 10$ abs.-coul. g.-equiv.$^{-1}$.
	$= 9651{\cdot}4_0 \pm 1{\cdot}0$ abs.-e.m.u. g.-equiv.$^{-1}$.
	$F' = Fc = (2{\cdot}89326 \pm 0{\cdot}00030) \times 10^{14}$ abs.-e.s.u. g.-equiv.$^{-1}$.
Avogadro number (chemical scale)	$N_0 = (6{\cdot}0228_3 \pm 0{\cdot}0011) \times 10^{23}$ mol.$^{-1}$.
Electronic charge	$e = F/N_0 = (1{\cdot}60203_3 \pm 0{\cdot}00034) \times 10^{-20}$ abs. e.m.u.
	$e' = ec = (4{\cdot}8025_3 \pm 0{\cdot}0010) \times 10^{-10}$ abs. e.s.u.
Specific electronic charge	$e/m = (1{\cdot}7592 \pm 0{\cdot}0005) \times 10^7$ abs.-e.m.u. g.$^{-1}$.
	$e'/m = ec/m = (5{\cdot}2736_6 \pm 0{\cdot}0015) \times 10^{17}$ abs.-e.s.u. g.$^{-1}$.
Planck constant	h (see table *c*).

TABLE *a'*.

Atomic Weights.

(1) Physical scale ($^{16}O = 16{\cdot}0000$).

$^1H = 1{\cdot}00813 \pm 0{\cdot}00001_7$. $^2H = 2{\cdot}01473 \pm 0{\cdot}00001_3$.

$H = 1{\cdot}00827_6 \pm 0{\cdot}00001_7$ (from $^1H/^2H$ abundance $= 6900 \pm 100$).

$^4He = 4{\cdot}00389 \pm 0{\cdot}00007$.

$^{12}C = 12{\cdot}00386 \pm 0{\cdot}00004$. $^{13}C = 13{\cdot}00761 \pm 0{\cdot}00015$.

$C = 12{\cdot}01465 \pm 0{\cdot}00023$ (from $^{12}C/^{13}C$ abundance $= 92 \pm 2$).

$^{14}N = 14{\cdot}00753 \pm 0{\cdot}00005$. $^{15}N = 15{\cdot}0049 \pm 0{\cdot}0002$.

$N = 14{\cdot}01121 \pm 0{\cdot}00009_5$ (from $^{14}N/^{15}N$ abundance $= 270 \pm 6$).

$^{16}O = 16{\cdot}0000$. $^{17}O = 17{\cdot}0045$. $^{18}O = 18{\cdot}0049$.

$O = 16{\cdot}00435_7 \pm 0{\cdot}00008_6$.

(from abundance $^{16}O : ^{18}O : ^{17}O = (506 \pm 10) : 1 : (0{\cdot}204 \pm 0{\cdot}008)$.

(2) Chemical scale ($O = 16{\cdot}0000$).

Ratio physical to chemical scale:

$r = (16{\cdot}004357 \pm 0{\cdot}000086)/16 = 1{\cdot}000272 \pm 0{\cdot}000005$.

$^1H = 1{\cdot}00785_8 \pm 0{\cdot}00001_8$ (from physical scale).

$^2H = 2{\cdot}01418_2 \pm 0{\cdot}00002_1$ (from physical scale).

$H = 1{\cdot}00800_2 \pm 0{\cdot}00001_8$ (from physical scale).

$^4He = 4{\cdot}00280 \pm 0{\cdot}00007$ (from physical scale).

$C = 12{\cdot}01139 \pm 0{\cdot}00024$ (from physical scale).

$N = 14{\cdot}00740 \pm 0{\cdot}00012$ (from physical scale).

$N = 14{\cdot}0086 \pm 0{\cdot}0007$ (direct observation).

$Na = 22{\cdot}994 \pm 0{\cdot}003$.

$Cl = 35{\cdot}457 \pm 0{\cdot}001$.

$Ca = 40{\cdot}080 \pm 0{\cdot}005$.

$Ag = 107{\cdot}880 \pm 0{\cdot}002$.

$I = 126{\cdot}915 \pm 0{\cdot}004$.

* Unless otherwise specified, all quantities in these tables that involve the mol. or the gram equivalent are on the chemical scale of atomic weights.

TABLE *b*.

Additional Quantities Evaluated or Used in Connection with Table a.

Ratio of e.s.u. to e.m.u. (direct).
$c' = (2{\cdot}9971_2 \pm 0{\cdot}0001) \times 10^{10}$ cm.$^{1/2}$ sec.$^{-1/2}$ int.-ohm$^{1/2}$.
$= (2{\cdot}9978_4 \pm 0{\cdot}0001_0) \times 10^{10}$ cm. sec.$^{-1}$.

Ratio of e.s.u. to e.m.u. (indirect).
$c' = c = (2{\cdot}99776 \pm 0{\cdot}00004) \times 10^{10}$ cm. sec.$^{-1}$.

Average density of earth	$\delta = 5{\cdot}517 \pm 0{\cdot}004$ g. cm.$^{-3}$.
Maximum density of water	$\delta_m(H_2O) = 0{\cdot}999972 \pm 0{\cdot}000002$ g. cm.$^{-3}$
Acceleration of gravity (standard)	$g_0 = 980{\cdot}665$ cm. sec.$^{-2}$.
Acceleration of gravity (45°)	$g_{45} = 980{\cdot}616$ cm. sec.$^{-2}$.
Density of oxygen gas (0° C., A_{45})	$L_1 = 1{\cdot}42897 \pm 0{\cdot}00003$ g. litre^{-1}.
Limiting density of oxygen gas (0° C., A_{45})	$L_{\lim} = 1{\cdot}427609 \pm 0{\cdot}000037$ g. litre^{-1}.
Factor converting oxygen (0° C., A_{45}) to ideal gas	$1-a = 1{\cdot}000953_5 \pm 0{\cdot}000009_4$.
International coulomb (= q abs. coul.)	$q = 0{\cdot}99986 \pm 0{\cdot}00002$.
International gauss (= q abs. gauss).	
International henry (= p abs. henry)	$p = 1{\cdot}00048 \pm 0{\cdot}00002$.
International volt (= pq abs. volt)	$pq = 1{\cdot}00034 \pm 0{\cdot}00003$.
International joule (= pq^2 abs. joule)	$pq^2 = 1{\cdot}00020 \pm 0{\cdot}00004_5$.
Specific gravity of Hg (0° C., A_0) referred to air-free water at maximum density	$\rho_0 = 13{\cdot}59542 \pm 0{\cdot}00005$.
Density of Hg (0° C., A_0)	$D_0 = 13{\cdot}59504_0 \pm 0{\cdot}00005_7$ g. cm.$^{-3}$.
Electrochemical equivalents (chemical scale) :	
Silver (apparent)	$E_{Ag}^* = 1{\cdot}11800 \times 10^{-3}$ g. int.-coul.$^{-1}$.
(corrected)	$E_{Ag} = (1{\cdot}11807 \pm 0{\cdot}00012) \times 10^{-3}$ g. abs.-coul.$^{-1}$.
Iodine (apparent)	$E_I^* = (1{\cdot}315026 \pm 0{\cdot}000025) \times 10^{-3}$ g. int.-coul.$^{-1}$.
(corrected)	$E_I = (1{\cdot}31535 \pm 0{\cdot}00014) \times 10^{-3}$ g. abs.-coul.$^{-1}$.
Effective calcite grating space (18° C.), Siegbahn system	$d''_{18} = 3{\cdot}02904 \times 10^{-8}$ cm.
True calcite grating space (20° C.), Siegbahn system	$d'_{20} = 3{\cdot}02951_2 \times 10^{-8}$ cm.
True calcite grating space (20° C.), c.g.s. system	$d_{20} = (3{\cdot}03567_4 \pm 0{\cdot}00018) \times 10^{-8}$ cm.
Ratio of grating and Siegbahn scales of wave-lengths	$\lambda_g/\lambda_s = 1{\cdot}002034 \pm 0{\cdot}000060$.
Density of calcite (20° C.)	$\rho = 2{\cdot}71029 \pm 0{\cdot}00003$ g. cm.$^{-3}$.
Structural constant of calcite (20° C.)	$\phi = 1{\cdot}09594 \pm 0{\cdot}00001$.
Molecular weight of calcite (chemical scale)	$M = 100{\cdot}091_4 \pm 0{\cdot}005$.
Rydberg constant for hydrogen (^{1}H)	$R_H = 109677{\cdot}581_2 \pm 0{\cdot}007_5$ cm.$^{-1}$ (I.A. scale).
Rydberg constant for deuterium (^{2}H)	$R_D = 109707{\cdot}419_3 \pm 0{\cdot}007_5$ cm.$^{-1}$ (I.A. scale).
Rydberg constant for helium	$R_{He} = 109722{\cdot}263 \pm 0{\cdot}012$ cm.$^{-1}$ (I.A. scale).
Rydberg constant for infinite mass	$R_\infty = 109737{\cdot}303 \pm 0{\cdot}017$ cm.$^{-1}$ (I.A. scale), or $\pm 0{\cdot}05$ cm.$^{-1}$ (c.g.s. system).

TABLE *c*.

Partial List of Derived Quantities.†

Planck constant :

$$h = \left\{\frac{2\pi^2c^3F^5}{R_\infty N_0^5(e/m)}\right\}^{1/3} = (6{\cdot}624_2 \pm 0{\cdot}002_4) \times 10^{-27} \text{ erg. sec.}$$

$$h/e = \left\{\frac{2\pi^2c^3F^2}{R_\infty N_0^2(e/m)}\right\}^{1/3} = (4{\cdot}1349_0 \pm 0{\cdot}0007_1) \times 10^{-7} \text{ erg. sec. abs.-e.m.u.}^{-1}.$$

$$h/e' = h/ec = \left\{\frac{2\pi^2F^2}{R_\infty N_0^2(e/m)}\right\}^{1/3} = (1{\cdot}3793_3 \pm 0{\cdot}0002_2) \times 10^{-17} \text{ erg. sec. abs.-e.s.u.}^{-1}$$

Atomic weight of electron : $E = F/(e/m)$.

(physical scale) $= (5{\cdot}4862_4 \pm 0{\cdot}0017) \times 10^{-4}$.
(chemical scale) $= (5{\cdot}4847_5 \pm 0{\cdot}0017) \times 10^{-4}$.

Band spectra constant connecting wave number and moment of inertia :

$$h/8\pi^2c = \left\{\frac{F^5}{256\pi^4R_\infty N_0^5(e/m)}\right\}^{1/3} = (27{\cdot}98_{65} \pm 0{\cdot}01_0) \times 10^{-40} \text{ g. cm.}$$

Boltzmann constant :

$$k = R_0/N_0 = V_0A_0/T_0N_0 = (1{\cdot}38047_4 \pm 0{\cdot}00026) \times 10^{-16} \text{ erg. deg.}^{-1}.$$

Charge in electrolysis of one gram of H :

$$F/\text{H} = 9572{\cdot}1_{72} \pm 1{\cdot}0 \text{ abs.-e.m.u. g.}^{-1}.$$

Charge in electrolysis of one gram of ^{1}H :

$$e/M_{1_H} = F/{}^1\text{H} = 9573{\cdot}5_{60} \pm 1{\cdot}0 \text{ abs.-e.m.u. g.}^{-1}.$$

† In order to be able to calculate, by propagation of errors, the probable error in a derived quantity, it is necessary to express the quantity explicitly in terms of the various fundamental quantities of Table *a* or of Table *b*, and that has been done in each case. Since in this paper e and h are treated as derived quantities, they do not therefore appear in such explicit expressions. But in calculating the *numerical* value of a derived quantity, the work can often be greatly simplified by using the values of other previously calculated derived quantities—in particular e and h. In order to show how certain derived quantities depend on quantities like e and h, such alternative expressions are given in many cases.

Compton shift at 90° :

$$h/mc = \left\{\frac{2\pi^2F^2(e/m)^2}{R_\infty N_0^2}\right\}^{1/3} = (0{\cdot}024265_{14} \pm 0{\cdot}000005_7) \times 10^{-8} \text{ cm.}$$

Energy in ergs of one abs.-volt-electron :

$$E_0 = 10^8 e = 10^8 F/N_0 = (1{\cdot}60203_3 \pm 0{\cdot}00034) \times 10^{-12} \text{ erg.}$$

Energy in calories per mol. for one abs.-volt-electron per molecule :

$$\frac{F \text{ (abs. coul. per gram-equiv.)}}{J_{15} \text{ (abs. joules per cal.)}} = 23052{\cdot}_{88} \pm 3{\cdot}_2 \text{ cal.}_{15} \text{ mol.}^{-1}.$$

Fine structure constant :

$$\alpha = 2\pi(e')^2/hc = \left\{\frac{4\pi R_\infty F(e/m)}{N_0}\right\}^{1/3} = (7{\cdot}2976_6 \pm 0{\cdot}0008_8) \times 10^{-3}.$$

$$1/\alpha = 137{\cdot}030_3 \pm 0{\cdot}016.$$

$$\alpha^2 = (5{\cdot}3256 \pm 0{\cdot}0013) \times 10^{-5}.$$

Gas constant per mol. :

$$R_0 = V_0A_0/T_0 = (8{\cdot}31436 \pm 0{\cdot}00038) \times 10^7 \text{ erg. deg.}^{-1} \text{ mol.}^{-1}.$$

$$R_0' = R_0 \,.\, 10^{-7}/J_{15} = 1{\cdot}98646_7 \pm 0{\cdot}00021 \text{ cal.}_{15} \text{ deg.}^{-1} \text{ mol.}^{-1}.$$

$$R_0'' = V_0'/T_0 = (8{\cdot}20544_7 \pm 0{\cdot}00037) \times 10^{-2} \text{ litre atmos. deg.}^{-1} \text{ mol.}^{-1}.$$

$$R_0''' = R_0/A_0 = V_0/T_0 = 82{\cdot}0566_7 \pm 0{\cdot}0037 \text{ cm.}^3 \text{ atmos. deg.}^{-1} \text{ mol.}^{-1};$$

also

$$R_0T_0 = V_0A_0 = (2{\cdot}27115_0 \pm 0{\cdot}00006) \times 10^{10} \text{ erg. mol.}^{-1}.$$

Loschmidt number (0° C., A_0) :

$$n_0 = N_0/V_0 = (2{\cdot}6870_{12} \pm 0{\cdot}0005_0) \times 10^{19} \text{ atmos.}^{-1} \text{ cm.}^{-3}.$$

Magnetic moment of one Bohr magneton :

$$\mu_1 = (h/4\pi)(e/m) = \frac{1}{4\pi}\left\{\frac{2\pi^3c^3F^5(e/m)^2}{R_\infty N_0^5}\right\}^{1/3}.$$

$$= (0{\cdot}9273_{45} \pm 0{\cdot}0003_7) \times 10^{-20} \text{ erg. gauss}^{-1}.$$

Magnetic moment per mol. for one Bohr magneton per molecule :

$$\mu_1N_0 = \frac{1}{4\pi}\left\{\frac{2\pi^2c^3F^5(e/m)^2}{R_\infty N_0^2}\right\}^{1/3} = 5585{\cdot}2_4 \pm 1{\cdot}6 \text{ erg. gauss.}^{-1} \text{ mol.}^{-1}.$$

Mass of α-particle :

$$M_\alpha = (\text{He} - 2\text{E})/N_0 = (6{\cdot}6442_2 \pm 0{\cdot}0012) \times 10^{-24} \text{ g.}$$

Mass of atom of unit atomic weight :

$$M_0 = 1/N_0 = (1{\cdot}66035 \pm 0{\cdot}00031) \times 10^{-24} \text{ g.}$$

Mass of electron :

$$m = e/(e/m) = (F/N_0)/(e/m) = (9{\cdot}1066_0 \pm 0{\cdot}0032) \times 10^{-28} \text{ g.}$$

Mass of ^{1}H atom :

$$M_{^1\text{H}} = {}^1\text{H}/N_0 = (1{\cdot}67339_3 \pm 0{\cdot}00031) \times 10^{-24} \text{ g.}$$

Mass of proton :

$$M_\text{P} = (^1\text{H} - \text{E})/N_0 = (1{\cdot}67248_3 \pm 0{\cdot}00031) \times 10^{-24} \text{ g.}$$

Radiation density constant :

$$a = 8\pi^5k^4/15c^3h^3 = \left(\frac{V_0A_0}{T_0}\right)^4 \frac{4\pi N_0^3R_\infty(e/m)}{15c^6F^5} = (7{\cdot}569_{42} \pm 0{\cdot}004_8) \times 10^{-15} \text{ erg. cm.}^{-3} \text{ deg.}^{-4}.$$

Ratio mass ^{1}H atom to mass electron :

$$M_{^1\text{H}}/m = (e/m)(^1\text{H}/F) = 1837{\cdot}5_{61} \pm 0{\cdot}5_6.$$

Ratio mass proton to mass electron :

$$M_\text{P}/m = (e/m)\left(\frac{^1\text{H} - \text{E}}{F}\right) = 1836{\cdot}5_{61} \pm 0{\cdot}5_6.$$

Second radiation constant :

$$c_2 = hc/k = \frac{T_0c^2}{V_0A_0}\left\{\frac{2\pi^2F^5}{R_\infty N_0^3(e/m)}\right\}^{1/3} = 1{\cdot}4384_8 \pm 0{\cdot}0003_4 \text{ cm. deg.}$$

Specific charge of α-particle :

$$2e/M_\alpha = \frac{2F}{\text{He} - 2\text{E}} = 4822{\cdot}3_3 \pm 0{\cdot}5_1 \text{ abs.-e.m.u. g.}^{-1}.$$

Specific charge of proton :

$$e/M_\text{P} = \frac{F}{^1\text{H} - \text{E}} = 9578{\cdot}7_7 \pm 1{\cdot}0 \text{ abs.-e.m.u. g.}^{-1}.$$

Stefan-Boltzmann constant :

$$\sigma = ac/4 = 2\pi^5k^4/15c^2h^3 = \left(\frac{V_0A_0}{T_0}\right)^4 \frac{\pi^3N_0R_\infty(e/m)}{15(Fc)^5}$$

$$= (5{\cdot}672_{83} \pm 0{\cdot}003_7) \times 10^{-5} \text{ erg. cm.}^{-2} \text{ deg.}^{-4} \text{ sec.}^{-1}.$$

Wave-length associated with one abs. volt :

$$\lambda_0 = 10^{-8}c^2(h/e') = \frac{c^2}{10^8}\left\{\frac{2\pi^2F^2}{R_\infty N_0^2(e/m)}\right\}^{1/3} = (12395{\cdot}_4 \pm 2{\cdot}_1) \times 10^{-8} \text{ cm. abs.-volt}$$

Wave number associated with one abs. volt :

$$s_0 = 1/\lambda_0 = \frac{10^8}{c^2}\left\{\frac{R_\infty N_0^2(e/m)}{2\pi^2F^2}\right\}^{1/3} = 8067{\cdot}4_9 \pm 1{\cdot}4 \text{ cm.}^{-1} \text{ abs.-volt}^{-1}.$$

Wien's displacement-law constant : *

$$A = c_2/4{\cdot}965114 = 0{\cdot}28971_8 \pm 0{\cdot}00007 \text{ cm. deg.}$$

Zeeman displacement per gauss :

$$(e/m)/4\pi c = (4{\cdot}6699_1 \pm 0{\cdot}0013) \times 10^{-5} \text{ cm.}^{-1} \text{ gauss.}^{-1}.$$

* The factor 4·965114 is the root of $e^{-\beta} + (\beta/5) - 1 = 0$.

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